International Journal of Psychosocial Rehabilitation, Vol. 24, Issue 02, 2020
ISSN: 1475-7192

Effect of Dual-Task Net Step Exercise on Working Memory, Global Cognitive Function and Brain Derived Neurotrophic Factor Serum Levels in Elderly with Mild and Moderate Cognitive Impairment

[1]Subagyo, [*1]Imam Subadi, [1]Asri Sulistyaningrum,[2]Purwo Sri Rejeki, [1]Meissy Andriana

ABSTRACT---Background: *Mild and moderate cognitive impairment in elderly lead to activity limitation and decrease quality of life. Brain derived neurotrophic factor (BDNF) levels is decreased in elderly with cognitive impairment. Physical exercise can promote cognitive function improvement. One of the mechanisms is through BDNF.*

Objective: *Analyzed the effect of dual-task Net Step Exercise (NSE) on working memory, global cognitive function and BDNF serum levels in elderly with mild and moderate cognitive impairment.*

Method: *The study was pretest-posttest control group design, which enrolled 26 elderly subjects with mild and moderate cognitive impairment, 13 subjects in intervention (dual-task NSE) group and 13 subjects in control group. Before and after study working memory, global cognitive function and serum levels of BDNF was examined quantitatively with enzyme linked immune-sorbent assay (ELISA).*

Result: *There was improvement of mini-mental state examination (MMSE) score ($p = 0.001$) and trail making test-B (TMT-B) score ($p = 0.03$) in intervention group after 8 weeks of dual-task NSE, while there was no improvement in control group. There was significant elevation of BDNF serum levels in intervention group after 8 weeks of dual-task NSE ($p<0.001$) while there was no significant change of BDNF serum levels in control group ($p = 0.107$).*

Conclusion: *Dual-task NSE could improve working memory and global cognitive function and also increase BDNF serum levels in elderly with mild to moderate cognitive impairment.*

Keywords---*BDNF, cognitive impairment, elderly, NSE*

I. INTRODUCTION

Mild to moderate cognitive impairment (MCI) is the intermediate stage between cognitive changes of normal aging and dementia. Human and animal studies have converged on the idea that physical exercise may beneficial for brain health and cognition. This effects achieved by certainly multiple reasons such as increase the flow of oxygenious-rich blood to the brain, stimulates neurogenesis and promote brain and synaptic plasticity(Cotman and

[1]*Departments of Physical Medicine & Rehabilitation Universitas Airlangga, dr. Soetomo General Hospital, Surabaya 60286, Indonesia*
[2] *Departments of Physiology Universitas Airlangga, Medical faculty of Universitas Airlangga, Surabaya 60131, Indonesia*
**Coresponding Author: Dr.Imam Subadi dr., Sp.KFR.*
Departments of Physical Medicine & Rehabilitation Universitas Airlangga, dr. Soetomo General Hospital, Surabaya 60286, Indonesia
Email: isubadi@gmail.com; imam.subadi.unair@gmail.com

DOI: 10.37200/IJPR/V24I2/PR200723
Received: 05 Jan 2020 | Revised: 20 Jan 2020 | Accepted: 30 Jan 2020

Berchtold, 2002; Blondell, Hammersley-Mather and Veerman, 2014). Working memory is part of cognitive system for temporarily storing and managing the information required to carry out complex cognitive tasks. Important information is gradually transferred from short-term into long term memory. The more the information is repeated or used, the more likely it is to eventually end up in long term memory, or to be retained. In elderly, neurodegenerative process deprives memory span(Mundkur, 2005).

A meta-analysis study has concluded that activity consist of both motoric and cognitive stimulation, in example dual-task activity, related to improvement of cognitive performance in elderly. The mechanism underlying is enhancement of long-term potentiating (LTP) process of memory, which persistent increase of synaptic strength following high-frequency or repetitive stimulation of a chemical synapse(Erickson *et al.*, 2010; Smith, Nielson and Antuono, 2013).

A number of studies have provided evidence that physical exercise can promote brain derived neurotrophic factor (BDNF), a certain protein generated in neurons, muscle and hematopoietic (Yulinda *et al.*, 2019) that plays role in neuronal survival and synaptic plasticity which are essential for learning and memory(Bathina and Das, 2015). BDNF found in high concentrations in the centralnervous system, primarily in the brain regions of the hippocampus, cerebral cortex,hypothalamus, and cerebellum(Praag *et al.*, 2005; Smith, Nielson and Antuono, 2013). Central BDNF can cross the blood-brainbarrier and therefore be stored in other areas of the body. BDNF has been implicated in neural development and functioning, including neurogenesis, dendritic growth, and long-term potential of neurons(Yamada and Nabeshima, 2003).Given the evidence for BDNF increases, exercise can be viewed as a potentialstrategy for inducing BDNF activity for application to the enhancement of cognition(Szuhany, Bugattia and Otto, 2015).

Net step exercise (NSE) is a novel dual-task walking program uses a net and features slow and low-impact physical movement and cognitive activity. In previous study dual-task NSE has been proven improve cognitive performance in healthy elderly. Dual-task NSE program has not been conducted in elderly with cognitive impairment subjects before. There were no previous study that examined BDNF serum levels after dual-task exercise, in particularly dual-task NSE. Therefore, this study aimed to analyze the effect of dual-task NSE on working memory, global cognitive function and BDNF serum levels as marker of cognitive function(Kitazawa *et al.*, 2015; Szuhany, Bugattia and Otto, 2015).

II. METHODS

This study was a non-randomized pretest and posttest control group design. The study was conducted in two nursing home care in Surabaya, WredaUndaan Nursing House and WredaJambangan Nursing House, February-April 2018. Twenty-six elder men and women who fulfilled the inclusion criteria were enrolled in the study. The intervention and control group consist of 13 subjects each. Subjects in intervention group received dual-task NSE twice a week for 8 weeks, while control group received education about mental health in elderly.

Inclusion criteria were men or women aged 60-75 years, mini-mental state examination (MMSE) score 15-26, good hearing and vision function, can understand and follow verbal instructions well, independent ambulation without assistive device, willing to participate in this research by signing the informed consent after obtaining an explanation.Criteria of drop out were less than 75% of total attendance should be followed, hemodynamic disturbance symptomize with fatigue or excessive sweating, drowsiness, tightness, pallor, or pulse rate exceeding the maximum

DOI: 10.37200/IJPR/V24I2/PR200723
Received: 05 Jan 2020 | Revised: 20 Jan 2020 | Accepted: 30 Jan 2020

heart rate, oxygen saturation < 95% or decrease 4 from baseline, blood pressure > 160/100, the subject declares to resign, died.

Trail Making Test Part B (TMT-B) were used to assessed working memory function. This test consists of 25 circles distributed over sheet of paper. The circles include both numbers (1-13) and letters (A-L). Subjects were asked to draw line to connect the circles in an ascending pattern, but with added task of alternating between the numbers and letters, as quick as possible without lifting the pen from paper. If subject makes an error, examiner has to point it out immediately and allow the subject to correct it. The time (in second) start from first circles after the end of circles counted as the TMT-B score. Global cognitive function was assessed with MMSE, and the BDNF serum levels was assessed one day before subjects began the exercise. BDNF levels in this study was measured quantitatively with enzyme linked immune-sorbent assay(ELISA) using reagensiaQuantukine ELISA Human Free BDNF (R&D System, Inc. Mineapolis, USA) Cat: DBD00, Lot: P166314, ED: @*th March 2019. Subjects were reevaluated after eight-weeks.

The dual-task NSE was conducted with 1 or 2 people at a time were required to walk carefully, but rhythmically from one end of the Fumanet to the other without stepping on the ropes or being caught in thenet. All participants were required to repeat the step designs in exactly the same way as their instructors. Throughout the 8-week NSE program, the difficulty ofthe step designs and the number of steps required in each session were gradually increased(Kitazawa *et al.*, 2015).

The statistical analyses were performed by using SPSS version 22.0 program. The differences in the parameters after the treatment were determined by using paired-sample *t*-test or Wilcoxon signed-rank test. The differences between the groups were determined by using independent-sample *t*-test and Mann–Whitney *U*-test. The *p* values less than 0.05 were accepted as statistically significant.The ethical appeal is submitted to the Medical Research Ethics Committee of the Faculty of Medicine, Airlangga University.

III. RESULT

All subjects received evaluation according to a predetermined schedule. No side-effects were found during and after intervention. Table 1 shows the characteristics of research subjects in both groups. Data analysis showed no significant differences in age, sex, body mass index (BMI), levels of education, MMSE score before intervention, but significant difference in TMT-B score between two group before intervention.

Table 2 shows changes of MMSE score and TMT-B score before and after treatment in both groups. The result of the intervention group which has been performed by dual task NSE shows the significant difference result.Table 3 shows that the change (delta) of MMSE score in intervention group significantly different with change (delta) in control group ($p = 0.009$). Change (delta) in TMT-B score was counted in percentage due to the inhomogen baseline. TMT-B score between two groups before exercise. Thechange (delta) of percentage of TMT-B score in intervention group significantly different with change (delta) in control group ($p < 0.001$).

Table 4 shows changes in BDNF serum levels before and after intervention in both groups. The BDNF serum levels mean in intervention group shows significant elevation of BDNF serum levels ($p < 0.001$).There is no significant change of BDNF serum levels in this group ($p = 0.107$). Significant different of change (delta) between intervention and control group (p=0,004) showed in Table.5.

DOI: 10.37200/IJPR/V24I2/PR200723
Received: 05 Jan 2020 | Revised: 20 Jan 2020 | Accepted: 30 Jan 2020

IV. DISCUSSION

The result of recent study has showed improvement in MMSE score after 8 weeks program in intervention group, but not in control group. There was also significant decreased of TMT-B score after program inintervention group. This means less time needed to finish the TMT-B worksheet, means improvement of time reaction and working memory. There were significantly difference between two groups in the change (delta) of MMSE score. Change in TMT-B score between both groups could not assessed in its absolut value because there was in homogenity TMT-B score in both groups before program, so the change was analyzed in percentage. There was improvement of TMT-B score for about 13.09±11.518% in intervention group, while in control group there was more time needed to finish the TMT-B worksheet for about 1.16±9.67% compares with before program.The result of the study is supported previous study from Kitazawa et al 2015 that conducted dual-Task NSE once a week for eight weeks in 60 healthy elderly subjects more than 70 years old in whichfound improvement of cognitive function about 6.8% (Kitazawa *et al.*, 2015).

All subjects in the study might follow other activity in their nursing home. Subjects in control group received education about mental health in elderly once in the beginning of the study and permitted to do their daily activities as before without receiving dual-task NSE program. There was no drop out and no reported incident of joint pain, fall or emergency until the end of study. The study conducted at two different nursing home to avoid interventional bias. Elderly subjects were recruited from nursing to have similarity in physical activity levels and nutritional intake.

According to statistical analysis, characteristic of sex, age, BMI, education, MMSE score, and BDNF serum levels were homogen between two groups. The exception was in TMT-B score that showed better score in control group. It can be caused by many factors. Some literatures have reported relationship between age and BDNF. In human, BDNF levels in circulation decreased significantly with increasing age. BDNF may be modulated in human through body composition. Study in 17 overweight and obese subjects that underwent 3 months of caloric restriction has showed increasing BDNF serum levels after program(Lommatzsch, 2005; Siuda, 2017).

In study that enrolled 118 healthy subjects, therewere no difference of BDNF serum levels between males and females. Otherwise, a cross sectional study involved 4463 elderly subjects had found significant difference of BDNF serum levels between males and females. This is caused by hormonal difference(Lang, 2004; Lommatzsch, 2005; Shimada *et al.*, 2014).Levels education, in means length of formal study counting from elementary education, will affect cognition that related to BDNF serum levels also. A study has reported association between low BNDF serum levels with lower cognitive test scores(Shimada *et al.*, 2014).

A functional MRI study has compared neural activities before and after dual-task exercise. The study showed decreased magnitude neural activities at several activated brain region and convergence of neural activities at prefrontal cortex area in the end of dual-task exercise training. This phenomenon representation cortical reorganization process involved neural efficiency after dual-task training become adept and specific.

The result of the change of BDNF serum levels after dual-task Nse showed significant elevation of 4828.23±3069.31pg/ml of BNDF serum levels in intervention group after dual-task NSE; otherwise no increased in control group.A meta-analysis study has reviewed 29 studies about effect of physical exercise on peripheral BDNF levels and conclude that aerobic type of exercise could increase plasma and serum BDNF, but not with resistance exercise(Ding, 2011).

DOI: 10.37200/IJPR/V24I2/PR200723
Received: 05 Jan 2020 | Revised: 20 Jan 2020 | Accepted: 30 Jan 2020

The normally very high concentration of BDNF in blood could be derived not only from the brain but also from peripheral sources, since body tissues express this growth factor. Given that cerebral BDNF crosses the BBB, it is reasonable to assume that the serum BDNF concentrations are associated with BDNF levels in the brain. The assumption is substantiated by animal experiment showing that BDNF serum levels are correlated with BDNF expression in cortical region(Gass, 2010).

Complex motor movement based physical exercise such as dual task has components motor learning, sensory integration, visual tracking and visual scanning. Motor learning or motor skill is body or extremities voluntary purposeful movement. There are attention and concentration needed in that motions. During the movement, vestibular system also stimulated, which can activate the formation reticularis at the brainstem and selecting relevant – irrelevant information and create awareness that support attention and concentration. Sensory integration is the brain ability to organize the information received from all body sensory modalities including auditory, visual and balance stimulations. Visual scanning and tracking are ability to observe and following the track. This component stimulates eye-extremities coordination.

Dual-task NSE is structured physical activity consist of complex motor movement that rich of stimulation and need attention and concentration. As example, when subject practicing NSE, they would miss the handclapping if they were concentrating on stepping over the net. However, if they were concentrating on handclapping, they would step incorrectly. Consequently, subject in the right square watching the net to perform the exercise correctly. Subjects also had to learn new step design each week.The limitation of this study is that assessment and monitoring of physical and social activity before and during study did not delivered. Post study evaluation of cognition and working memory function was done by the researcher so emerge examiner bias. Further study must be conducted in randomized design.

V. CONCLUSION

Dual-task NSE twice a week can improve the working memory and cognitive function and also elevate the BDNF serum levels in elderly with mild moderate cognitive impairment.

REFERENCE

[1] Bathina, S. and Das, U. (2015) ‘Brain-derived neurotrophicfactorand its clinical implications’, *Arch Med Sci*, 11(6), pp. 1164–1178.

[2] Blondell, S., Hammersley-Mather, R. and Veerman, J. (2014) ‘Does physical activity prevent cognitive decline and demensia?: A systematic review and meta-analysis of longitudinal studies’, *BMC Public Health*, 14(1), pp. 1–12.

[3] Cotman, C. and Berchtold, N. (2002) ‘Exercise: A Behavior intervention to enhance brain health and plasticity’, *Trends in Neurosciences*, 25(6), pp. 295–300.

[4] Ding, Q. (2011) ‘Exercise Influences Hippocapal Plasticity by Modulatng Brain-derived Neurotrophic Factor Processing’, *Nuroscience journal*. UK: Department of Experimental Psychology, Oxford University, OXI 3UD, 192, pp. 773–780.

[5] Erickson, K. *et al.* (2010) ‘Brain-derived neurotrophic factor is associated with age-related decline in hippocampal volume’, *J Neurosci*, 30, pp. 5368–75.

[6] Gass, P. (2010) ‘Pheripheral Brain-Derived Neurotrophic Factor (BDNF) as a biomarker for affective disorder?’, *The International Journal of Neuropsychopharmacology*, 13, pp. 1–4.

[7] Kitazawa, K. *et al.* (2015) ‘Effect of a Dual-task Net-Step Exercise on Cognitive and Gait Function in Older Adults’, *Journal of Geriatric Physical Therapy*, 38(3), pp. 133–140.

[8] Lang, U. (2004) ‘BDNF Serum Concentrations in Healthy Volunteers are Associated with Depression-Related Personality Traits’, *PubMed Neuropsychopharmacology Journal*, 29, pp. 795–798.

DOI: 10.37200/IJPR/V24I2/PR200723
Received: 05 Jan 2020 | Revised: 20 Jan 2020 | Accepted: 30 Jan 2020

[9] Lommatzsch, M. (2005) 'The impact of Age, Weight and Gender on BDNF levels in Human Platelets and Plasma', *Neurobiology of Aging Journal*, pp. 115–123.
[10] Mundkur, N. (2005) 'Neuroplasticity in Children', *Indian Journal Pediatri*, 72(10), pp. 855–7.
[11] Praag, H. *et al.* (2005) 'Exercise Enhance Learning and Hippocampal Neurogenesis in Aged Mice', *J Neuroscience*, 25(38), pp. 8680–5.
[12] Shimada, H. *et al.* (2014) 'A Large, Cross-Sectional Observational Study of Serum BDNF, Cognitive Function, and Mild Cognitive Impairment in the Elderly', *Frontiers in Aging Neuroscience*, 6(69), pp. 1–9.
[13] Siuda, J. (2017) 'Cognitive Impairment and BDNF Serum Levels', *PubMed NeurolNeurochir*, 51(6), p. 537.
[14] Smith, J., Nielson, K. and Antuono, P. (2013) 'Semantic Memory functional MRI and cognitive function after exercise intervention in mild cognitive impairment', *Journal of Alzheimers Disease*, 37, pp. 197–215.
[15] Szuhany, K., Bugattia, M. and Otto, M. (2015) 'A meta-analytic review of the effects of exercise on brainderivedneurotrophic factor', *Journal of Psychiatri Res*, 60, pp. 56–64.
[16] Yamada, K. and Nabeshima, T. (2003) 'Brain Derived Neurotrophic Factor/TrkB Signaling in Memory processes', *Journal of Pharmacological Science*, 91(4), pp. 267–270.
[17] Yulinda, S. *et al.* (2019) 'Brain Derived Neurotropic Factors in Speed vs. Inclined Treadmill in Young Adult Healthy Male With Occult Balance Disorder', *Frontiers in Integrative Neuroscience*, 13.

Table 1: Baseline characteristics

Characteristic	Control group (n = 13)	*dual-task* NSE group (n = 13)	*P*
Sex (%)			
Male	46.2	69.2	0.427
Female	53.8	30.8	
Age (year)	73 (62-75)	70 (60-75)	0.495
BMI (kg/m^2)	25.08±6.274	22.91±3.373	0.286
Levels of education (year)	7.46±3.152	6.30±3.146	0.360
MMSE score	20.46±3.950	19.076±4.152	0.392
TMT-B (second)	327.07±144.099	439.38±96.18	0.044

Levels of significance p <0.05

Table 2: Changes in MMSE score and TMT-B score before and after 8 weeks at intervention and control group

Variable	***Pre-***	***Post-***	***P***
Intervention group (n=13)			
MMSE score	19.07±4.152	22.00±5.244	0.001
TMT-B score (second)	430.38±96.684	373.84±102.737	0.003
Control group (n=13)			
MMSE score	20.46±3.950	21.15±3.578	0.069

DOI: 10.37200/IJPR/V24I2/PR200723
Received: 05 Jan 2020 | Revised: 20 Jan 2020 | Accepted: 30 Jan 2020

TMT-B score (second)	327.07±144.099	329.07±144.162	0.712

Levels of significance p <0.05

Table 3:Change (delta) MMSE score and TMT-B score in both group

Variable	**Group**		***P***
	Intervention (n = 13)	**Control (n = 13)**	
MMSE	2.92±2.431	0.69±1.250	0.009
TMT-B (%)	-13.3523 (-34.07 – (-0.36))	0.7407 (-13,54 – 27.06)	<0.001

Levels of significance p <0.05

Table 4: Changes in BDNF serum levels before and after 8 weeks at intervention and control group

Variable	***Pre-***	***Post-***	**P**
Intervention group (n=13)			
BDNF levels (pg/dl)	25520.23±6428. 26	30348.46±7234.73	<0.001
Control group (n=13)			
BDNF levels (pg/dl)	26947.69±7881.43	28193.76±8942.53	0.107

Levels of significance p <0.05

Table 5: Delta BDNF serum levels in both group

Variable	**Group**		**P**
	Intervention(n=13)	**Control(n=13)**	
BDNF levels (pg/dl)	4828.23 ± 3069.31	1246.07 ± 2576.98	P = 0.004

Levels of significance p <0.05

DOI: 10.37200/IJPR/V24I2/PR200723
Received: 05 Jan 2020 | Revised: 20 Jan 2020 | Accepted: 30 Jan 2020