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Evaluation of Real Brain Activity Using an Ultra-Compact Brain Activity Sensor for the Assessment of Cognitive Function

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Abstract

This study aimed to verify the selection process for the program intended for use during an intervention study and the efficiency of the program content before starting the intervention study for the purpose of improving cognitive function. We confirmed real time cortical hemodynamics in the dorsolateral prefrontal cortex (DLPFC) with participants wearing an ultra-compact brain activity sensor (XB-01), and verified the program to be introduced during the intervention study. The participants were a total four of healthy adults, two women and two men aged in their 20's through 50's. During the experiment, the participants wore XB-01 connected to the iPhone using Bluetooth for the collection of data. XB-01 data indicating the brain activity (blood flow) during the program was demonstrated by real time color changes on the connected iPhone to evaluate the results on a 100 point scale. We examined 21 programs in total, including those reported to increase brain activity. We conducted an analysis of variance for each of the four programs detected in the upper and lower regions for comparing brain activity, which resulted in finding a main effect of the program ($F_{(7,21)}=4.35$, $p < 0.05$). An exercise program including a dual task with large limb movements was highly effective in increasing brain activity in the DLPFC. Moreover, slightly higher speed, pace, and difficulty level of the program most suitable for participants were more effective. Brain activity increased in the DLPFC during the program and several minutes after its completion. These findings can help develop programs that prevent and improve cognitive function. This verification study revealed that the introduction or creation of such programs appeared to facilitate the activation of DLPFC and thereby increase DLPFC activity.

Keywords: Dementia; Physical exercise; Dual task; Event related potentials; Cortical hemodynamics; Exercise program

Introduction

The World Health Organization (WHO) [1] reported approximately 50 million worldwide dementia cases in September 2020, with a gradual increase of approximately 10 million new cases every year. The estimated global cost (direct and indirect financial burden on healthcare) of dementia is $ 818 billion, which is expected to increase to $ 2 trillion by 2030. Hence, WHO has declared dementia prevention and treatment a public health priority; simulation studies [2,3] suggest that even delaying disease onset by 2 years would have substantial public health, economic, and societal benefits. Decreased cognitive functions are associated, among other factors, with vascular factors and depressive disorders [4]. Multiple long term follow up studies have explored the connection between physical activity and dementia, including the LADIS (Leukoaraiosis and Disability) [5] and the Rotterdam [6] studies. Asada [7] reported that the most evidenced method for preventing dementia includes exercise, followed by Web mediated cognitive training. Plassman et al. [8] analyzed 172 observational studies and 22 randomized controlled trials (RCTs), evaluating the effect of exercise and cognitive training. Walking was the most used method for exercise interventions among the 22 RCTs. Several cohort studies have reported the preventive effect of late life physical exercise on cognitive deterioration. An 8 year-long study on elderly Taiwanese adults [9] examined the relationship between exercise and cognitive function and indicated that a 30-min exercise session reduced the risk of cognitive decline. Kawashima [10] studied the age related control of cognitive functions. Age related cognitive decline may occur due to linear decline in the prefrontal cortex function. Executive function is the core of various higher cognitive activities and requires the cooperative operation of various brain areas. As dementia and other cognitive developmental disorders may impair executive function, we hypothesized that it could be improved by introducing certain training methods demonstrated to maintain and improve the brain function (prefrontal cortex function) in healthy aged people. Patients with amnestic mild cognitive impairment (aMCI) and frontal executive dysfunction have poor prognosis and should be given a higher priority for intervention therapy among patients with aMCI [11]. Funahashi et al. [12] explained that executive function is a product of coordinated operation of multiple neural systems and an essential prerequisite for a variety of cognitive functions, and the prefrontal cortex is known to be a key structure for the performance of executive functions. Executive function has also been reported to help with resisting temptation and making it mentally possible to play with ideas such as suppression and interference control, working memory, and cognitive flexibility [13]. A study of secondary results from an RCT on the effects of exercise on memory in older adults with probable mild cognitive impairment has supported the prevailing notion that exercise can positively impact cognitive function and may represent an effective strategy to improve memory in those who have begun to experience cognitive decline [14]. In a study on brain derived neurotrophic factor (BDNF), the interaction of estrogen, physical activity, and hippocampal BDNF was demonstrated to be important for maintaining brain health, plasticity, and general well-being, particularly in women [15]. Furthermore, physical exercise was effective in reducing proinflammatory cytokines and improving BDNF peripheral levels, with positive effects on cognition [16]. The applicability of primary functional brain imaging modalities to cognitive neuroscience has been confirmed by performing cognitive tasks on a computer and combining magnetic resonance imaging (MRI) with a method for examining performance such as key press responses [17]. However, there are issues associated with MRI such as limited movement, noise, high cost, and the requirement for specialized knowledge. Moreover, it is hard to test out the programs in real time due to the abovementioned problems. These factors are delaying progress in brain science as well as treatment against dementia. However, the ultra-compact brain function measurement device "XB-01" hereinafter referred to as XB-01; length 80 mm, width 40 mm, thickness 13 mm, and weight 30 g released by NeU Inc., a brain science company jointly launched by Tohoku University and Hitachi High Tech in 2018, made it possible to measure brain activity changes in real daily life situations (Figure 1).

Figure 1 The ultracompact brain function measurement device "XB-01". Copyright by NeU Inc.

By measuring changes in cortical hemodynamics with weak near infrared light, this device can visualize the state of brain activity by measuring changes in the concentration of oxygenated and deoxygenated hemoglobin, pulse rate, and acceleration. This device uses near infrared spectroscopy, which irradiates active brain areas with near infrared light and detects the returning near infrared light as a proxy for changes in hemoglobin levels in the blood circulating in the brain to assess changes in blood oxygenation and cerebral blood flow. Herold et al [18]. Focus on the application of functional near infrared spectroscopy (fNIRS), since this neuroimaging modality provides specific advantages, making it well suited for monitoring cortical hemodynamics as a proxy of brain activity during physical exercise. In addition, to enhance user experience, this device is set and the user is not required to set the measurement frequency and wavelength to be used. This device is ultra-compact and has a limited measurement range, but unlike conventional devices, it does not have a cord, so noise is less likely to enter and the effect of artifacts is small. These real time measurements help determine the type of exercise program that can be effective in increasing brain activity and efficiently develop an efficient intervention program. Most studies on brain activity using this device were performed on the memorization of numbers and calculation problems performed on the screen, but few studies focused on body exercises, whereas few neurological studies have reported real time brain activity using XB-01. In this study, we hypothesized that there was no significant difference between upper and lower scores in the score of brain activity in DLPFC evaluated by XB-01 for programs that reportedly showed brain activity and those that claimed to increase brain activity. We hypothesized that, among the programs to be verified, walking presented with the highest score of brain activity in DLPFC evaluated by XB-01. This study aimed to verify the selection process of the program intended for use during the intervention study and the efficiency of the program content before starting the intervention study for the purpose of improving cognitive function. We confirmed real time cortical hemodynamics in the DLPFC with participants wearing an ultra-compact brain activity sensor, and verified the program to be introduced during the intervention study.

Materials and Methods

Participants were recruited by excluding individuals with severe depression, cognitive impairments, cardiovascular disease, etc. and those who were anxious about participating in the program. We selected four participants: two healthy women (age: 26, 52 years) and two healthy men (age: 34, 52 years) aged 20–50 years. As the study was conducted during the coronavirus disease 2019 pandemic, it was conducted on a small number of people to prioritize the participants' safety. This participant group was not linked to dementia, but they lived near the institute and were supportive of dementia prevention program research. The program lasted from June 7 to July 4, 2020. Given the preliminary

Figure 2 The participants wore a precharged XB-01 with a headband a little over the left eyebrow on the forehead. Copyright by NeU Inc.

nature of the study, no control group was set; similar studies have been performed on other populations. Before the experiments, the purpose and methods of this study were fully explained to the participants, and written informed consent to participate in the experiment was obtained. The experiment was performed with the approval of the research ethics committee at PCY, Ltd. (approval number 20-2). The experiment was conducted in a room available for exercise at a room temperature (20°C). During

Figure 3 XB-01 data indicate real-time brain activity (blood flow volume) during the exercise program by color changes on the screen of the connected iPhone. The color changed to red for high and to blue for low brain activity. Copyright by NeU Inc.

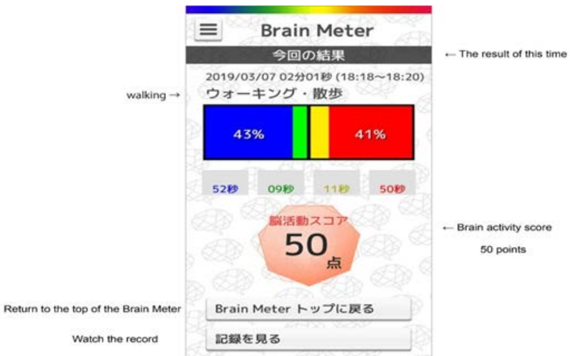

Figure 4 Brain activity results on a 100-point scale were evaluated. Copyright by NeU Inc.

[Partially revised by the author.]

the experiment, the participants wore a precharged XB-01 with a headband a little over the left eyebrow on the forehead and connected to an iPhone using Bluetooth for data collection (Figure 2).

The Active Brain CLUB app (hereinafter referred to as ABCa, NeU Inc., Tokyo, Japan) to the iPhone was downloaded and the function called Brain Meter was stated; then, it was paired with XB-01. XB-01 data indicate real time brain activity (blood flow volume) during the exercise program by color changes on the screen of the connected iPhone. The color changed to red for high and to blue for low brain activity (Figure 3). Brain activity results on a 100 point scale were evaluated (Figure 4).

The score of this Brain Meter was preset by Tohoku University and Hitachi High Tech, and ABCa automatically displayed the score on the iPhone screen according to the activity state of the brain. Data were collected by dividing 21 programs into 3 days and conducting the programs for 1 hour per participant per day. The participants were questioned about the presence of any adverse effect such as musculoskeletal pain on each exercise session. Furthermore, the instructors monitored participants for symptoms of angina and shortness of breath during the exercise classes. We examined each exercise program including one recognized to increase brain activity [7,19], which included the following elements:

A Walking: Participants walked on a treadmill for 3 min at 6 km/h with a wide stride and strong arm swing.

B Raising the thigh: On the spot, the participants raised the thigh on each side alternatively 30 times up to waist height.

C Self weight strength training [20]: The participants performed this exercise for approximately 2 min while watching a video. First, their hands were crossed in front of their chest with their knees and toes facing outward, and their legs spread more than twice their shoulder width apart. Slowly, from this position, they lowered their hips and moved up and down 20 times while contracting their buttocks. Then, with their legs spread more than twice their shoulder width apart, they lowered their hips with their elbows placed on the inside of their knees. For 10 s, they closed the knees with all their strength and then opened them, with the elbows simultaneously doing a similar movement.

D Synapsology [21]: For approximately 3 min while watching a video, the participants performed a program of movements only for the upper body. Synapsology is an original program developed by Renaissance, Inc. First, they learned three movements directed by numbers. If the instructor said 1, they placed their right hand on their head and their left hand on their waist. If 2, they placed their left hand on their head and their right hand on their waist. If 3, they placed their hands on their shoulders. Next, the numbers directed by the instructor changed to colors. Instead, of 1, 2, and 3, the instructor directed them by naming colors: red, yellow, and blue. Finally, the color indicated by the instructor was changed to a visual stimulus. When the instructor showed red, yellow, and blue balls, the participants said the colors simultaneously aloud with movements.

E Brain training exercises to prevent dementia (Web version): The participants underwent memory training for approximately 4 min while watching a computer screen. After memorizing the pictures one by one, they watched the video and got the assignment (Table 1).

TABLES

Table 1. Brain-training exercises to prevent dementia (Web version of the task)

What day is May 5th?

What time is it now?

Calculate 27 × 8.

Which photos did they see earlier among many photos?

F Droutability: Total 10 programs were performed with two Vision Drout program types. Droutability is derived from the “Draw out Ability” coordination exercise program devised by Dr. Yasumitsu [22]. Vision Drout is a program performed while looking at the monitor.

F 1 Program performed using a Drout cross (a cross shaped training tool). The participants stood at a cross mark placing on the floor in front of them and performed the four programs while watching the video.

F 1-1 After a circle appeared on the screen; they moved their right foot to that position of the cross and stood there on one foot. After a triangle appeared, they moved their left foot to that position of the cross.

F 1-2 After a circle appeared on the screen, they squatted down, touched their right hand to that position on the cross, and stood there. After a triangle appeared, they did the same with their left hand.

F 1-3 At the beginning, they acted similarly to F 1-1, and in the middle, after the blue cross appeared on the screen, they performed the movement for phase F 1-2. After the second appearance of the blue cross on the screen, they performed the movement for F 1-1, thus alternating the movements for F 1-2 and F 1-1.

F 1-4 The participants performed the program as in F 1-3 with hands and feet switched: circles correspond to left foot and hand and triangles to right foot and hand.

F 2 Programs to move, stop, and up and down.

While watching the computer screen, the participants underwent a practice program, followed by both (a) and (b).

a) While “Move” was shown on the screen, they stepped in the spot with large movements of their arms and legs. During “Stop,” they stopped and stood upright. During “Up,” they lightly jumped and clapped their hands once on their head while saying “up.” During “Down,” they squatted down; while saying “down,” they put their hands on the floor and stood up fast. The participants performed three programs at three different speeds-F 2-a-1: slow, F 2-a-2: normal, and F 2-a-3: fast.

b) While "Move" was shown in green on the screen, they stepped in the spot with large movements of their arms and legs. During "Move" in red, they stopped perfectly and stood upright.

During "Stop" in green, they stopped perfectly and stood upright. During "Stop" in red, they stepped in the spot with large moving their arms and legs.

During "Up" in green, they jumped lightly and clapped their hands once on their head while saying "up." During "Up" in red, they squatted down; while saying down, they placed their hands on the floor and stood up fast.

During "Down" in green, they squatted down; while saying down, they placed their hands on the floor and stood up fast. During "Down" in red, they jumped lightly and clapped their hands once on their head while saying "up."

The participants performed three programs at three different speeds-F 2-b-1: slow, F 2-b-2: normal, and F 2-b-3: fast.

G Spot the Differences: We used p92–p93 in "Spot the Differences to Train Your Brain" [23]. The participants were seated and performed the test for 1 min using two sheets of paper.

H Crossword: We used p20–p21 of the March 2020 issue of Crossword Mate [24]. The participants were seated and performed the test for 1 min using two sheets of paper.

I Radio Exercise No. 1: The participants exercised for about 3.5 min while watching a video. "Radio exercise" is a physical exercise routine, which every Japanese person learns in their childhood.

J Kickboxing: The participants performed for 3 min including an explanation and practice interval while watching the video. They performed a middle kick with their front foot, followed with their back foot, for 60 s each.

K Tai chi: The participants performed the movements for about 3 min while watching a movie. They performed the movements of "Introductory Taijiquan," Taijiquan for beginners.

L Boxing [25]: The participants performed for 4 min including an explanation and practice interval while watching the video. First, they performed a one–two, next to webbing, followed by one–two webbing.

Before the start of all programs, they performed deep breathing for 15 s. Moreover, they required to remain stationary until receiving the finish signal at the end of the program. When the color of the brain activity turned blue on the iPhone screen and remained so for ≥ 5 s, we gave the signal to end the program. Statistical processing software (IBM SPSS Statistics 24) was used to test the difference in mean values among groups in each calculation item. We performed a one way within participants analysis of variance (ANOVA) for each of the four programs at the maximum and minimum values. We performed multiple comparisons by the Bonferroni method for items with significant F values. We set the significance level at 5%.

Results

In this study, we examined the brain activity levels produced by the 21 programs in the 12 categories. In Table 2 compares their brain activity scores and score rankings. A one factor ANOVA was performed for each of the four upper and lower programs in the detected score rankings to compare brain activity. As a result, the main effect of the program was recognized ($F(7,21) = 4.35$, $p<.05$). The data were normally distributed. The highest score was in the exercise program using dual tasks.

Table 2. Brain activity scores and rankings

Program	Means	SD	Rankings
A	54	9.27	17
B	56.5	10.88	13
C	46.25	11.27	20
D	56	7.87	14
E	55	11.2	16
F 1-1	43.75	4.03	21
F 1-2	57.25	5.91	12
F 1-3	61.75	15.17	3
F 1-4	55.25	11.59	15
F 2-a-1	61.25	9.64	4
F 2-a-2	58	15.3	8
F 2-a-3	59	13.83	5
F 2-b-1	64.5	8.51	1
F 2-b-2	57.5	19.6	11
F 2-b-3	52.25	5.97	19
G	58	6.27	9
H	58.25	10.28	7
I	57.75	1.5	10
J	64.25	5.32	2
K	52.75	5.19	18
L	58.5	5.51	6

Discussion

As a result of this study, the hypothesis that there was no significant difference between upper and lower levels in the score of brain activity in DLPFC evaluated by XB-01 was not supported in the program that was reported to recognize brain activity and the program which was said to increase brain activity. Furthermore, our outcomes did not support the hypothesis that walking was the highest score for brain activity in DLPFC evaluated by XB-01 in the program to be verified. Despite walking being used as an exercise intervention method in many previous studies on dementia [26], the scores of walking were intermediate in this study. Treadmill exercise can impact the hippocampal histone acetylation profile in an age and lysine dependent manner [27], suggesting that prolonged exercise increases the capillary reserve. Capillary growth occurs in motor areas of the cerebral cortex as a robust adaptation to prolonged motor activity [28]. The Life Randomized Trial was conducted on 1,635 people at risk of cognitive impairment; however, among sedentary older adults, a 24 month moderate intensity physical activity program compared with a health education program did not result in improvements of the global or domain specific cognitive function [29]. We did not get high scores in exercises performed with slow movements such as strength training with body weight and tai chi. Previous studies [30] have reported that slow and relaxed movements do not activate the DLPFC. We reported lower scores if exercise programs using the dual task were too easy and higher scores if the speed and thinking pace increased. However, we observed a lower score if the difficulty level was too high or the speed too fast. Kawashima [30] considered the act of thinking to be the most complex activity and to require the cooperation of many brain regions, but only using a portion of the left prefrontal cortex and that brain activity was low during meditating. We reported higher scores when the movements during the program included large motions using limbs, such as bending, stretching, and kicking, but not for unconscious and familiar movements such as radio exercise. We reported lower scores if there were any negative factors such as pain in parts of the body during knee flexion/extension or other movements, or small letters that were difficult to see. In the case of dementia, which often affects the middle aged and elderly people, it is necessary to develop and introduce a program that considers these factors. Negative emotions during cognitive training interfere with the improvement of cognitive function by training [31]. It has also been reported that positive mood during exercise affects the activation of the prefrontal cortex and the benefits of exercise for executive performance [32]. In this study, we confirmed that scores increased when the participants performed the program with painless knees. Summarizing previous cognitive neuroscience studies [33] recommended aerobic exercise at an intensity ≥75% HRR for 30–40 min, thrice a week over 3–6 months to improve cognitive function in the elderly. Considering this study, cognitive function could be impacted by increasing the DLPFC activity even with light load short time daily exercises, which the aged can more easily perform. Tachibana et al. also used fNIRS to verify the cortical hemodynamics during an actual motor task with a block design in which a dance video game alternates between 30 seconds of activity and 30 seconds of rest, and reported its effects [34]. Event related potentials (ERPs) are transient brain fluctuations temporally related to external or internal events, and greatly vary among individuals. In the present study, we identified various cases of blood flow changes in the DLPFC. Cortical hemodynamics could remain elevated for a long time although they often appear to be rising and falling. Often, we could observe increased brain activity during the program. On the other hand, interestingly, we could find many cases that did not increase during the program, but increased with the score after the program, suggesting that the brain was still active immediately after the program. This result is similar to previous studies [35] reporting that after 20 minutes of moderate intensity cycling, cortical oxygenation persisted for at least 15 minutes and aerobic exercise may promote neuroplasticity. Colcombe et al. [36] reported that it is possible to identify task related brain activated regions and the dynamics of neural activity when observing neural activity (cerebral hemodynamics) during conducting a cognitive task by functional MRI (fMRI). In this study, by using XB-01, we could confirm the brain activity in the DLPFC and detect ERPs difficult to characterize by fMRI. Many studies have reported the effects of cortical hemodynamics and exercise on the prefrontal cortex using fNIRS [37-41]. However, fNIRS methods and analysis and reporting of data vary greatly across studies which in turn can limit the replication of research, interpretation of findings, and comparison across works [42]. In addition, fNIRS is limited to cortical layers and strongly influenced by systemic physiological artifacts. Vitorio et al. reported the difficulty of measuring fNIRS during exercise, saying that conducting fNIRS studies while walking poses considerable technical and methodological challenges and may lead to inconsistent study results [43]. However, it was suggested that the ultra-compact brain activity sensor used in this study can easily measure the cortical hemodynamics of DLPFC like other fNIRS, although the measurement range is limited. This research made it possible to select the program to be introduced in advance. This is a feasibility study to test a new equipment. The activity of DLPFC can be efficiently enhanced by creating and introducing a program in advance with the contents of the program that scored high in this study. Being able to select and introduce a program that promotes brain activity in advance is very beneficial in promoting the improvement of cognitive function. In the future, larger sample sizes will be needed to detect the effect of each exercise program on brain activity. There are limitations to this study, including the small number of samples, the fact that the participants were only from 20–50 years age group, and that only blood flow changes in the DLPFC were confirmed. In future, we want to increase the number of participants to improve the accuracy of the study, verify the results in participants aged ≥50 years, and examine the effectiveness of these exercise programs in preventing and improving dementia. One disadvantage of the verified program is that it is intended for people who can move to some extent, and it is difficult to introduce it to people with a limited range of motion or those who cannot freely move their bodies. In future, we will examine the programs with high scores and develop highly effective programs for dementia prevention implementing them at facilities for the elderly, nursing homes.

Conclusion

An exercise program including a dual task with large limb movements was highly effective to increase brain activity in the DLPFC. Moreover, a slightly higher speed, pace, and difficulty level of the program most suitable for participants was reported to be more effective. Brain activity increased in the DLPFC not only during the program but also several minutes after its completion. These results show that they can contribute to the development of programs that help prevent and improve cognitive function. It was suggested that DLPFC can be activated efficiently by introducing or creating these programs, which are likely to increase the activity of DLPFC, as revealed by this verification.

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Disclosure of interest

The authors report no conflict of interest.

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