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Influence of Mobile Application Based Brain Training Program on Cognitive Function and Quality of Life in Patients Post Stroke

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Abstract

Background: *Stroke often leads to cognitive impairment, which can significantly reduce one's independence as well as quality of life. Cognitive rehabilitation is a treatment strategy for restoring cognitive abilities following brain injuries. Cognitive functioning can be improved through the use of multimedia as well as informatics in computerized cognitive rehabilitation (CCR).* **Purpose:** *to investigate the influence of a mobile application-based brain training program on cognitive functions as well as quality of life in post stroke patients.* **Methodology:** *forty referred medically and radiologically diagnosed stroke patients from both genders experienced post stroke cognitive impairment (PSCI), aged from 45 to 60 years old, were randomized into two groups of the same number: a study group and a control group.* ***The Study group*** *received mobile application-based brain training program (Lumosity training application) as well as aerobic training on a bicycle ergometer, and* ***the control group*** *received only the aerobic training on a bicycle ergometer for 18 sessions every other day for 6 weeks, 3 sessions/week, each session for 60 minutes. All patients were evaluated with Computer-based cognitive device RehaCom, Addenbrooke's Cognitive Examination Revised (ACE-R) test, Montreal Cognitive Assessment (MoCA) in addition to Stroke specific quality of life scale (SS-QoL) pre and post treatment.* **Results:** *a significant difference has been detected among the two groups as the (p-value = 0.001) indicating that the study group reported enhancement in the cognitive functions as well as the quality of life more than the control group and there was a correlation between RehaCom, MoCA, ACE-R and SS-QoL.* **Conclusion:** *This study showed that six weeks of mobile application-based brain training program (Lumosity training application) as well as aerobic training on a bicycle ergometer was a beneficial approach and is a successful treatment for patients suffering from (PSCI).*

Keywords: *Post stroke cognitive impairment, Computer-based cognitive device RehaCom, Addenbrooke's Cognitive Examination Revised (ACE-R) test, Montreal Cognitive Assessment (MoCA) and Stroke specific quality of life scale (SS-QoL).*

1. Introduction

Stroke refers to a clinical condition characterized by the sudden onset of a localized neurological impairment due to vascular injury (infarction, hemorrhage) affecting the central nervous system. Worldwide, stroke is the 2nd largest reason for death as well as disability. There is no single disease that causes stroke; rather, several different variables, diseases, and mechanisms can all contribute to the development of this condition. Ischemic strokes account for the vast majority (85%) of all strokes, with arteriolosclerosis, cardioembolism, as well as atherothromboembolism being the most common causes. Intracerebral bleeding, which can occur in the deep basal ganglia, brainstem, or cerebellum, accounts for about 15% of all strokes worldwide **(1).**

Greater than a third of stroke survivors develop cognitive problems, and it can occur at an earlier stage in some cases. Many people with this impairment struggle with it for a long time. It's linked to increased disability and lower functional independence, social engagement, as well as quality of life. Stroke survivors often have difficulties with memory, orientation, as well as attention. Effective measures that reduce the impact of post-stroke dementia, such as optimal post-acute stroke care as well as secondary prevention of cognitive drop, are required **(2).**

A novel approach to stroke rehabilitation is the creation and usage of mobile applications that help stroke survivors in enhancing their own self-management. Stroke survivors can benefit from a rehabilitation program that utilizes mobile applications since they can continue their treatment at home after their discharge from the hospital **(3)**

Improved performance on a wide variety of cognitive tasks, including speed, accuracy, visual-motor integration, focus, memory, and executive function have been observed in several BTG intervention studies **(4-8).**

Aerobic physical exercise (PE) has a potential role in reducing cognitive impairment after stroke. A number of different neural mechanisms, such as enhanced synaptic plasticity, the dendritic arborization, the growth and survival of adult-born neurons (neurogenesis), the reorganization of neural networks and compensation processes in surviving brain areas, angiogenesis, as well as reduced secondary injury and neuron damage, have been linked to the advantages of aerobic physical exercise on cognitive recovery following a stroke **(9).**

So, the current study was designed to investigate the impact of mobile application-based brain training program on cognitive functions as well as quality of life in post stroke patients.

2. Materials And Methods

The current study was conducted to examine the influence of the mobile application-based brain training program on cognitive functions as well as quality of life in post stroke patients. All patients were diagnosed clinically and radiologically and referred from their neurological consultants as having post stroke cognitive impairment (PSCI). The patients were chosen, and the study was carried-out in outpatient clinics of Faculty of physical therapy, Cairo and Badr Universities, this study was conducted at the period from January 2022 to December 2022.

True experimental research design study (one factorial RCT, pre-test and post-test control group design) was utilized. One trained research assistant assessed all patients and collected all data to reduce inter-investigator error. Patients were randomized according to the treatment procedure into two equal groups.

Randomization method: Patients who met the study's inclusion criteria were randomized into two groups (I and II) utilizing a secure opaque closed envelope allocation mechanism. **Group I (study group):** consisted of twenty right-handed hemiparetic patients received mobile application-based brain training program using the Lumosity training application on the smartphone as well as aerobic training on a stationary bicycle ergometer for 18 sessions every other day for 6 weeks, 3 times per week, every session for 1 hour (30 minutes aerobic training on a stationary bicycle ergometer followed by 30 minutes for Lumosity training application on the smartphone). **Group II (control group):** consisted of twenty right-handed hemiparetic patients received the aerobic training on the stationary bicycle ergometer only for 18 sessions every other day for 6 weeks, 3 sessions/week, each session for 1hour.

Blinding: All patients were assessed and referred by the same physician and physical therapy evaluation before beginning and at the end of the treatment program. Treatment allocations were kept secret from both the researcher and the participants.

Inclusion criteria: Forty right-handed hemiparetic patients from both genders aged from 45 to 60 years old. They are complaining from a single ischemic stroke due to vascular insult in the territory of the carotid system diagnosed by Neurologist and confirmed radiologically by CT and / or MRI of the brain. Duration of illness ranged from three to 18 months. Spasticity grade (1 to 1+) based on the Modified Ashworth Scale (MAS). Patients were diagnosed medically as mild cognitive impairment with score from (18-23) based on Mini Mental State Examination (MMSE). All patients have mild cognitive deficits with score <26 according to Montreal Cognitive Assessment scale, Cognitive function less than 82 according to Addenbrookes' Cognitive Examination- Revised [ACER]. Medically as well as psychologically stable patients. All patients had normal and stable vital signs (heart rate, blood pressure, temperature as well as respiratory rate). All patients had a good educational level and the body mass index ranged from 20-30 Kg/m2.

Exclusion criteria: Patients with Recurrent stroke or hemiparesis due to other neurological causes rather than stroke. Patients with severe cardiovascular issues (unstable angina, serious coronary heart disease, or congestive heart failure) that have not been adequately treated. Visual, auditory and other neurological disorders (eg: Multiple sclerosis, Parkinsonism…etc). Patients receiving medications that may affect cognition. Patients having Moderate and severe obesity (BMI $\geq$ 30 kg/m^2) and Illiterate patients.

Data collection and intervention

Assessment methods

After being informed of the study's goals, methods, potential benefits, privacy, as well as data use, all participants signed a written consent form. Pre-treatment and post-treatment assessments were conducted on all patients.

Assessment of cognitive function by Reha-com device

The computerized Reha-Com device containing the (attention and concentration) program was utilized as the patient is asked to concentrate on every detail in the separately presented picture and select the one that resembles it in every detail from the matrix, as the assessment screen is splitted into two parts. One portion represents the matrix that involves: according to (24) levels of difficulty: 3 pictures (1 by 3 matrix), 6 pictures (2 by 3 matrix) as well as 9 pictures (3 by 3 matrix), and the other part represents the separated picture.

Addenbrooke's Cognitive Examination Revised (ACE-R) test

It consists of 26 tasks, divided into five domains. It takes about 15 minutes to administer. The maximum possible score is 100, and questions are asked in the sequence stated, with scores calculated immediately based on the addition of point values for each correctly answered question **(10).**

Montreal Cognitive Assessment Scale (MoCA):

The test is commonly used to screen for cognitive impairment. It was designed to detect mild cognitive Impairment. It takes approximately 10 minutes to complete, 30-point cognitive screening instrument. It is utilized to evaluate multiple aspects of cognition, including: short-term memory; visual-spatial skills; executive function; concentration; attention; memory for work; language; as well as time-and-place awareness. The possible range of MoCA scores is 0–30. If you scored 26 or more, you're in the normal range. Scores below 25 indicate mild cognitive impairment (MCI) in individuals who have suffered a stroke, and the score has a high sensitivity (77%) as well as specificity (83%) **(11).**

Intervention methods

In the current study, the experimental group also received the 30-minute session of aerobic training given to the control group then the mobile application-based brain training program on lumosity training application for another 30 min, three times per week for six weeks.

The Lumosity cognitive training program was utilized as the treatment condition in this study. Training sessions will include three cognitive training tasks each of them target a particular core cognitive capability and are grouped into three categories by target domain: memory (working memory), attention (selective attention), and problem solving (logical reasoning) through these games (organic order and fues clues for logical reasoning training, lost in migration, trouble brewing, assist ants and train of thought for attention training and memory match and memory match one drive for working memory training). Tasks were provided in clusters over days, with no individual tasks being repeated on any one day, and the three tasks for a specific session were selected using an algorithm that aimed at maximizing a balance of training activities. it took about 30 minutes to finish a session consisting of all three tasks **(12).**

The control group of the present study received only the aerobic training that done on a stationary bicycle ergometer for 60 min (20 min training on the bicycle then 10 min. rest then another 20 min. training on the bicycle). three times per week for six weeks. Before starting the training procedure each patient was instructed to sit vertically on the bicycle ergometer seat with erect back. Extra strap was placed on patient's feet to provide complete fixation on ergometer pedal. in the first week, patients bicycled to tolerance at 40% to 50% max HR, and then progressed to the 70% max HR in the second week. Intensity of aerobic exercise was systematically progressed for each patient by increasing resistance to maintain conditioning at 70% max HR **(13).**

Statistical analysis

The effects of ACE-R, MoCA, and focus and attention were compared both within and across groups using a two-way mixed MANOVA. Bonferroni adjustments were made for further multiple comparison. All statistical tests were performed at the $p < 0.05$ level of significance. The Windows version 25 of the Statistical Package for the Social Sciences (SPSS) (IBM SPSS, Chicago, IL, USA) was used for all statistical analysis.

3. Results and Discussion

Effect of treatment on ACE-R, MoCA and attention and concentration

A significant interaction between treatment and time was found using two-way mixed MANOVA ($F = 25.83$, $p = 0.001$). The main impact of time was highly significant ($F = 449.99$, $p = 0.001$). Specifically, therapy had a statistically significant main impact ($F = 8.56$, $p = 0.001$).

Within group comparison

After treatment, both Group A and Group B showed statistically significant increases in ACE-R and MoCA relative to baseline ($p < 0.001$). The percentage increases in ACE-R and MoCA were 20.39 and 45.86 in group A, while it was 14.41 and 21.98 in group B, respectively. (Table 1).

The attention as well as concentration levels of both Group A and Group B significantly improved after treatment compared to before treatment ($p < 0.001$). After treatment, both Group A and Group B had significantly shorter minimum reaction time MRTs than they had before treatment ($p < 0.001$). (Table 2).

Between group comparison

No significant difference has been detected among groups pre-treatment ($p > 0.05$). There was a significant rise in ACE-R as well as MoCA of group A in comparison with that of group B post treatment ($p < 0.001$). A significant improvement has been detected in attention as well as concentration levels of group A in comparison with that of group B post treatment ($p < 0.01$). There was a significant decline in MRT of group A in comparison with that of group B post treatment ($p < 0.01$). (Table 1-2).

Table 1. Mean ACE-R and MoCA pre and post treatment of group A and B:

	Group A	Group B		
	Mean ±SD	Mean ±SD	MD	p value
ACE-R				
Pre treatment	76.50 ± 2.23	75.30 ± 2.67	1.2	0.13
Post treatment	92.10 ± 3.33	86.15 ± 3.24	5.95	0.001
MD	-15.6	-10.85		
% of change	20.39	14.41		

	p = 0.001	***p = 0.001***		
MoCA				
Pre treatment	19.95 ± 3.39	20.25 ± 3.04	-0.3	0.77
Post treatment	29.10 ± 1.55	24.70 ± 2.15	4.4	0.001
MD	-9.15	-4.45		
% of change	45.86	21.98		
	p = 0.001	***p = 0.001***		

SD, Standard deviation; MD, Mean difference; p value, Probability value.

Table 2. Mean attention and concentration levels and MRT pre and post treatment of group A and B:

	Group A	**Group B**		
	Mean ±SD	**Mean ±SD**	**MD**	**p value**
Attention and concentration level				
Pre treatment	2.55 ± 0.82	2.40 ± 0.68	0.15	0.53
Post treatment	4.80 ± 0.95	3.15 ± 0.93	1.65	0.001
MD	-2.25	-0.75		
% of change	88.24	31.25		
	p = 0.001	***p = 0.001***		
MRT (msec)				
Pre treatment	7368.9 ± 888.53	7156.40 ± 916.54	212.5	0.46
Post treatment	2847.70 ± 597.99	4214.80 ± 734.65	-1367.1	0.001
MD	4521.2	2941.6		
% of change	61.36	41.10		
	p = 0.001	***p = 0.001***		

SD, Standard deviation; MD, Mean difference; p value, Probability value

This study showed that the combination between the mobile application-based brain training program using the lumosity training application on the smartphone and aerobic training on a stationary bicycle ergometer was more effective for improving cognitive dysfunctions as well as quality of life in post stroke patients having cognitive disorders in the study group than utilizing the aerobic training only in the control group.

Post-stroke cognitive impairment (PSCI) refers to any cognitive deficits that become apparent between three and six months after the occurrence of a stroke. It involves not just preexisting deficiencies, but also those caused by the stroke itself, including aphasia or memory loss, and impairments resulting from strategic infarcts in the hippocampus, the thalamus, and important cortical regions. Cognitive screening after a stroke typically identifies higher-order visuospatial, attentional, as well as executive problems, which is more strongly linked to classic vascular cognitive impairment (VCI) **(14).**

Mobile apps are rising to prominence as a type of digital therapies as a result of the growing popularity of smartphones around the world and the subsequent shift to telemedicine in response to the COVID-19 epidemic. Given the limitations of traditional one-on-one sessions with physiotherapists, the use of cognitive training via mobile apps has emerged as a potentially useful complement **(15).**

Consistent with the findings of Yeh et al., 2019 (2), the present study discovered that a 12- to 18-week sequential training program which sequentially combined aerobic exercise as well as computerized cognitive training significantly enhanced cognitive capabilities as well as motor functioning in patients with cognitive impairment following stroke. Improvements in general cognitive skills (measured by MoCA scores) characterize the improvement, which is consistent with our own MoCA-based findings.

This study's findings provide support to the idea that a mobile app-based brain training program can improve the quality and efficiency of rehabilitation for those with neurological disorders like stroke. Repetitive cognitive tasks, rapid presentation of stimuli using multisensory stimulation, and an increase in neural plasticity (involving both structural as well as functional changes in the brain) are just a few of the potential advantages associated with using pc-cognitive retraining in a rehabilitation setting after brain injury. Cognitive training has been shown to improve brain function as well as functional recovery by increasing the amount of grey matter and enhancing activity in subcortical areas. Using computer-based trainings, therapists can help patients regain some of their lost cognitive function **(16).**

Cognitive impairment caused by aging and mild cognitive impairment following stroke can be reduced through interventions that combine the incorporation of aerobic physical exercise (PE) with cognitive training, as revealed by Amorós-Aguilar et al., (2021) (17), and supported by the findings of the current study. Stroke-related cognitive impairment may additionally be treated by cognitive rehabilitation treatments and aerobic physical exercise only. Combining these types of actions can seem to make the greatest impact.

The findings of the current study were consistent with those of Ozen et al. (2021) (18), who presented video game systems as novel and appealing interventions. Cognitive function increased in the control group that received both physical and occupational treatment. Experimental exercises, physiotherapy, as well as specialized computer gaming difficulties helped individuals in both groups. In terms of motor function, the hemiplegic upper extremity improved in both groups, whereas the hand improved only in the experimental group. The agreement with this study was referred to the same choice of the sample size problem and the same matrix of assessment tools used in our study as both of us found improvement in the scores of MoCA and SS-QoL scales.

Additionally, Nie et al. (2022) (19) proposed that computer assisted cognitive rehabilitation (CACR) can be a helpful tool for cognitive rehabilitation following stroke, and the results of the present study support this idea. It's effective for enhancing patients' ADL and cognitive abilities and recovering patients' general functional state. As specialists in the field of cognitive rehabilitation, you feel assured that you have enough data to safely and effectively use CACR to treat patients who have experienced a stroke.

Connor et al. (2012) (20) examined five individuals who had all suffered a severe stroke in the right hemisphere between the ages of 63 and 73, and their findings were at conflict with those of the present study. Brain-training games were recommended in the study to help individuals who have acquired brain injuries regain the cognitive abilities that had been damaged. The research recommended participants to complete 40 sessions of Lumosity training at least once each week for 15-30 minutes. The primary goal of the study was to determine whether or not neuroplasticity would change; but the study had to shift its focus because the participants were unable to complete all 40 sessions as a result of cognitive as well as physical impairments. According to the findings, individuals who have suffered a severe stroke would not benefit from this type of training. So due to the limited sample size, different age range and the prolonged time of rehabilitation the results of his study were in contradiction with our study results.

Contrary to the findings of Gaitán et al. (2012) (21), who found that adding a Computer-based cognitive training (CBCT) program to cognitive training (CT) for patients suffering from amnestic multi-domain MCI and AD improved anxiety symptoms as well as decision making but didn't appear to have a significant impact on cognitive functioning, the present study found no such effect and the cause of disagreement was referred to the difference in the sample size problem as our study worked with stroke patients while this study worked with Alzheimer patients.

4. Conclusion

According to the scope and results of this study, that concluded that the rehabilitation program of the study group that depends on mobile application-based brain training program using the Lumosity training application on the smartphone in addition to aerobic training on the stationary bicycle ergometer showed a significant enhancement in the cognitive function outcomes and the quality of life compared to the control group who received the aerobic training on the stationary bicycle ergometer only, so the present study indicates that mobile application-based brain training program is beneficial in improvement of cognitive functions, functional independency as well as quality of life of post stroke patients. Therefore, physiotherapy clinics should recommend a combination of the mobile application-based brain training program with the aerobic exercise as an efficient, reliable as well as noninvasive approach for rehabilitation.

References:

1. Murphy SJ and Werring DJ. (2020). Stroke: causes and clinical features. Medicine (Abingdon). Sep;48 (9):561-566. doi: 10.1016/j.mpmed.2020.06.002.
2. Yeh TT, Chang KC, Wu CY. (2019). The Active Ingredient of Cognitive Restoration: A Multicenter Randomized Controlled Trial of Sequential Combination of Aerobic Exercise and Computer-Based Cognitive Training in Stroke Survivors with Cognitive Decline. Arch Phys Med Rehabil. May;100(5):821-827.
3. Xuan Zhou, Minxia Du & Lanshu Zhou. (2018). Use of mobile applications in post-stroke rehabilitation: a systematic review, Topics in Stroke Rehabilitation, DOI: 10.1080/10749357.2018.1482446.
4. Toril, P., Reales, J. M., & Ballesteros, S. (2014). Video game training enhances cognition of older adults: A meta-analytic study. Psychology and Aging, 29, 706–716.
5. McDougall S and House B. (2012). Brain training in older adults: Evidence of transfer to memory span performance and pseudo-Matthew effects. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 19(1–2):195–221.
6. Janssen G, van Aken L, De Mey H, et al. (2014). Decline of executive function in a clinical population: age, psychopathology, and test performance on the Cambridge Neuropsychological Test Automated Battery (CANTAB) Appl Neuropsychol Adult. 21(3):210–19.
7. Leckie RL, Weinstein AM, Hodzic JC, Erickson KI. (2012). Potential moderators of physical activity on brain health. J Aging Res. 948981.
8. Kramer AF and Erickson KI. (2007). Capitalizing on cortical plasticity: Influence of physical activity on cognition and brain function. Trends Cogn Sci. 11(8):342–48.
9. Li, F.; Geng, X.; Huber, C.; Stone, C.; Ding, Y. (2020). In Search of a Dose: The Functional and Molecular Effects of Exercise on Post-Stroke Rehabilitation in Rats. Front. Cell. Neurosci. 14, 186.
10. Mioshi Eneida; Dawson Kate; Mitchell Joanna; Arnold Robert; Hodges John R. (2006). The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. 21(11), 1078–1085. doi:10.1002/gps.1610.
11. Nasreddine ZS, Phillips NA, Bédirian V, et al. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc.* 53(4):695-9. doi:10.1111/j.1532-5415. 53221. x.
12. Hardy JL, Nelson RA, Thomason ME, Sternberg DA, Katovich K, Farzin F, et al. (2015). Enhancing Cognitive Abilities with Comprehensive Training: A Large, Online, Randomized, Active- Controlled Trial. PLoS ONE 10(9): e0134467. doi:10.1371/journal. pone.0134467
13. Quaney BM, Boyd LA, McDowd JM, Zahner LH, He J, Mayo MS, Macko RF. (2009). Aerobic exercise improves cognition and motor function poststroke. Neurorehabil Neural Repair. 2009 Nov;23(9):879-85. doi: 10.1177/1545968309338193. Epub Jun 18. PMID: 19541916; PMCID: PMC3024242.
14. Dichgans, M., & Leys, D. (2017). Vascular cognitive impairment. *Circulation research*, *120* (3), 573-591.
15. Abbadessa, G., Brigo, F., Clerico, M., De Mercanti, S., Trojsi, F., Tedeschi, G. & Lavorgna, L. (2022). Digital therapeutics in neurology. Journal of Neurology, 269(3), 1209-1224.
16. Nguyen, L., Murphy, K., & Andrews, G. (2019). Cognitive and neural plasticity in old age: A systematic review of evidence from executive functions cognitive training. Ageing research reviews, 53, 100912.
17. Amorós-Aguilar, Laura, Erica Rodríguez-Quiroga, Sara Sánchez-Santolaya, and Margalida Coll-Andreu. (2021). "Effects of Combined Interventions with Aerobic Physical Exercise and Cognitive Training on Cognitive Function in Stroke Patients: A Systematic Review" *Brain Sciences* 11, no. 4: 473. https://doi.org/10.3390/brainsci11040473
18. Ozen, S., Senlikci, H. B., Guzel, S., and Yemisci, O. U. (2021). Computer game assisted task specific exercises in the treatment of motor and cognitive function and quality of life in stroke: A randomized control study. J. Stroke Cerebrovasc. Dis. 30:105991. doi: 10.1016/j.jstrokecerebrovasdis.2021.105991.
19. Nie P, Liu F, Lin S, Guo J, Chen X, Chen S, Yu L, Lin R. (2022). The effects of computer-assisted cognitive rehabilitation on cognitive impairment after stroke: A systematic review and meta-analysis. J Clin Nurs. May;31(9-10):1136-1148. doi: 10.1111/jocn.16030.
20. Connor, B. B., & Standen, P. J. (2012). So much technology, so little time: factors affecting use of computer-based brain training games for cognitive rehabilitation following stroke.
21. Gaitán A, Garolera M, Cerulla N, Chico G, Rodriguez-Querol M, Canela-Soler J. (2012). Efficacy of an adjunctive computer-based cognitive training program in amnestic mild cognitive impairment and Alzheimer's disease: a single-blind, randomized clinical trial. Int J Geriatr Psychiatry. 2013 Jan;28(1):91-9. doi: 10.1002/gps.3794. Epub 2012 Apr 3. PMID: 22473855.