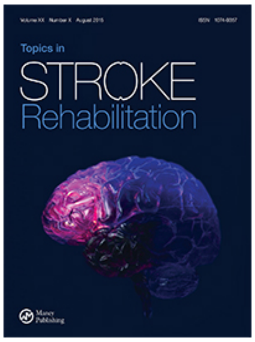

Topics in Stroke Rehabilitation

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ytsr20

Clinical efficacy of aerobic exercise combined with computer-based cognitive training in stroke: a multicenter randomized controlled trial

Ting-Ting Yeh, Ku-Chou Chang, Ching-Yi Wu, Chao-Jung Chen & I-Ching Chuang

To cite this article: Ting-Ting Yeh, Ku-Chou Chang, Ching-Yi Wu, Chao-Jung Chen & I-Ching Chuang (2021): Clinical efficacy of aerobic exercise combined with computer-based cognitive training in stroke: a multicenter randomized controlled trial, Topics in Stroke Rehabilitation, DOI: 10.1080/10749357.2021.1922045

To link to this article: https://doi.org/10.1080/10749357.2021.1922045

Published online: 02 Aug 2021.

TOPICS IN STROKE REHABILITATION
https://doi.org/10.1080/10749357.2021.1922045

Clinical efficacy of aerobic exercise combined with computer-based cognitive training in stroke: a multicenter randomized controlled trial

Ting-Ting Yeh[a,b], Ku-Chou Chang[c,d,e,f], Ching-Yi Wu[a,g,h], Chao-Jung Chen[a], and I-Ching Chuang[a,g,h]

[a]Department of Occupational Therapy and Graduate Institute of Behavioral Sciences, College of Medicine, Chang Gung University, Taoyuan, Taiwan; [b]Master Degree Program in Healthcare Industry, College of Medicine, Chang Gung University, Taoyuan, Taiwan; [c]Division of Cerebrovascular Diseases, Department of Neurology, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan; [d]College of Medicine, Chang Gung University, Taoyuan, Taiwan; [e]Discharge Planning Service Center, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan; [f]Department of Senior Citizen Service Management, Yuh-Ing Junior College, Kaohsiung, Taiwan; [g]Healthy Aging Research Center, Chang Gung University, Taoyuan, Taiwan; [h]Department of Physical Medicine and Rehabilitation, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan

ABSTRACT

Purpose: The objectives are to evaluate the effects of a sequential combination of aerobic exercise and cognitive training, compared with exercise or cognitive training alone, on cognitive function, physical function, daily function, quality of life, and social participation in stroke survivors with cognitive impairment.

Methods: This is a single-blind, parallel, randomized controlled trial. Stroke patients with mild cognitive impairment (n = 56) were randomly assigned to aerobic exercise training (n = 18), computerized cognitive training (n = 18), and the sequential combination of aerobic exercise and computerized cognitive training (n = 20) group. All groups underwent training 60 min/day, 3 days/week, for a total of 12 weeks. The primary outcomes included Montreal Cognitive Assessment (MoCA), Wechsler Memory Scale-Third Edition, and the Stroop color-word test. Secondary outcomes were the Timed Up and Go test, 6-Minute Walk Test, Functional Independence Measure, Lawton Instrumental Activities of Daily Living Scale, Community Integration Questionnaire, and Stroke Impact Scale.

Results: 56 participants completed the trial. Compared with a single type of aerobic exercise or cognitive training, the combined training group showed significant improvement in MoCA ($P < .05$, $\eta 2 = 0.13$), and two sub-tests in WMS-III (both P's < 0.05) following the intervention. However, no between-group differences were observed for physical functions, daily function, quality of life, and social participation measures.

Conclusions: The findings provide evidence for the potential synergistic intervention in stroke survivors. Future studies investigating the transfer effects and the optimal training parameters with a larger sample is needed.

ARTICLE HISTORY
Received 7 October 2020
Accepted 21 April 2021

KEYWORDS
Aerobic exercise; cognitive training; computer-based cognitive training; sequential training; stroke

Introduction

Cognitive disabilities are often the most disabling and distressing for stroke survivors, caregivers, family members, and society.[1] Persistent cognitive deficits after stroke can significantly impair independence, activities of daily living (ADL), and active participation in the community.[2] Post-stroke cognitive impairment and rehabilitation have been recognized as a top research priority.[3] A systematic review showed computer-based cognitive training is likely to provide some benefit in cognitive functions for stroke survivors.[4] The improvements in computer-based cognitive training were training specific (i.e. only outcomes similar to those tasks trained improved). Physical exercise is another intervention that may contribute positively by attenuating a decline in cognitive function in stroke survivors.[5] A systematic review examined whether physical exercise interventions improved cognitive function after stroke; a meta-analysis of nine studies showed a significant improvement in cognitive function with an effect size of 0.20.[5] The authors suggested that aerobic exercise may increase the arousal level and reduce depressive symptoms, which in turn leads to better cognitive function (e.g. higher scores on the Mini-Mental State Examination, MMSE).[5] Another systematic review confirmed the beneficial role of

CONTACT Ching-Yi Wu cywu@mail.cgu.edu.tw Healthy Aging Research Center, Department of Occupational Therapy & Graduate Institute of Behavioral Sciences, College of Medicine, Chang Gung University, Taoyuan, Taiwan

aerobic exercise in multiple domains of cognitive functions such as global cognitive ability and a potential benefit to memory, attention, and the visuospatial domain of cognition.[6]

The combination of different training approaches might be the most promising strategy to delay cognitive decline and preserve cognitive abilities. A review of multidomain interventions suggests that strategies that target multiple factors, such as exercise, mental training, and weight management, may be more effective in reducing cognitive decline in older adults than those focusing on a single factor.[7] Physical activity and cognitive training might interact to induce a larger functional benefit in elderly individuals.[8] Liu-Ambrose experimented with a 6-month exercise and recreation program on executive functions in individuals with chronic stroke and found that the combined exercise and recreation program significantly benefited executive functions in individuals who were mildly cognitively impaired.[9] The potential to further enhance cognitive training benefits is to 'prime' the brain by delivering aerobic exercise training prior to cognitive training. Aerobic exercise may increase arousal level, facilitate neurogenesis, and enhance memory consolidation, which may be more responsive to cognitive intervention protocols that follow.[10,11]

Specific training effects of cognitive training and physical exercise training on cognitive functions in older adults and patients with Mild Cognitive Impairment (MCI) are well documented; however, there is limited but promising evidence on the investigation of the combined effect of cognitive and physical training in stroke survivors with cognitive impairment. There is a need to take into account whether a combined approach may lead to additive effects in monotype approaches and spontaneous recovery. The present randomized trial evaluated the effects of a sequential combination of aerobic exercise and cognitive training, compared with exercise or cognitive training alone, on cognitive function, physical function, daily function, quality of life, and social participation in stroke survivors with cognitive impairment. We hypothesized that the combination of aerobic exercise and cognitive training would induce more beneficial cognitive and physical effects and would transfer to daily function, quality of life, and social participation than pure cognitive and physical interventions alone.

Materials and methods

This randomized trial used a 2 × 3 factorial design that evaluated the clinical effectiveness of a sequential combination program of aerobic exercise combined with computer-based cognitive training for the treatment of cognitive dysfunction after stroke (see study protocol[12]). The study recruited stroke survivors with cognitive impairment who were randomly divided into three groups: an aerobic exercise training group (AE), a cognitive training group (COG), and a sequential combination of aerobic exercise and cognitive training (SEQ). The randomization scheme was generated with the web-based Research Randomizer randomization tool (available at http://www.randomizer.org/). All participants received face-to-face individualized training in the hospitals by certified physical and/or occupational therapists for 60 minutes per day, 3 days per week for 12 weeks. Each participant completed a total number of 36 sessions.

Ethical considerations

This study was approved by the centralized ethics committee (IRB# 104-4892A3) and registered at ClinicalTrials.gov Identifier: NCT02550990. Written informed consent was obtained from all participants prior to their participation in the study. The design and reporting of this study follows the CONSORT (Consolidated Standards of Reporting Trials) guidelines.

Participation and recruitment

This study was conducted in the outpatient units of the Departments of Neurology and Rehabilitation at Chang Gung Memorial Hospitals at five branches (Taoyuan, Chiayi, Kaohsiung, Keelung, and Taipei) in Taiwan. Participants were recruited via a clinic database based on diagnosis and medical referrals; interested participants met with the study personnel to receive all necessary information. The participants resolved uncertainties and were invited to sign informed consent after an assessment of eligibility criteria. The inclusion criteria were (1) unilateral ischemic or hemorrhagic stroke occurring at least 6 months before enrollment; (2) age between 20 and 90 years; (3) Mini-Mental State Examination (MMSE) score ≥19; (4) Montreal Cognitive Assessment (MoCA) <26; (5) self-reported or informant-reported memory or cognitive complaints or Clinical Dementia Rating Scale (CDR) score ≤0.5; (6) able to follow the study instruction; (7) adequate cardiopulmonary function to perform the aerobic exercise; and (8) able to walk with or without assistive devices for 10 m. Participants were excluded if they (1) had an unstable medical history such as recent myocardial infarction that might limit participation; (2) had other neurologic disorders; or (3) currently participate in other clinical trials. A priori power analysis (G*Power software 3.1) was used to estimate the number of participants needed for this project. On the basis of Kim et al.,[13] the estimated sample size requirement is 15 patients for each group in a three-group study design given the lowest effect size (f = 0.30), power of 0.80, and two-sided type I error of 0.05. Allowing for 10% attrition at the end of the intervention, we planned to recruit 18 participants for each group.

Clinical intervention

AE training

The participants in the AE group performed progressive resistive stationary bicycle training[14] (Figure 1). The participants first underwent 10 minutes of warm-up, followed by 45 minutes of resistive aerobic exercise, followed by 5 minutes of cool-down. The target heart rate during the aerobic period was 40–70% of the participant's maximal heart rate (HR_{max}), calculated as (208 − 0.7 × age).[15] The exercise intensity progressed as the participants improved their performance. The exercise intensity was increased from the initial 40–50% gradually increased to 60–70% HR_{max} over the 12 weeks. The therapist monitored closely for any adverse effects of the increased exercise intensity and downward adjustments if the exercise is not tolerated during the session.

COG training

The participants in the COG group received computer-based cognitive training using BrainHQ software (Posit Science Inc., San Francisco, CA, USA)[16] (e.g. BrainHQ software includes different training programs that are designed to restore attention, recognition, color and shape identification, calculation, visual perception, visuospatial processing, memory, and executive function). Participants performed a variety of tasks designed to enhance different cognitive functions. During the training sessions, laptops with touchscreens were provided so that the participants performed the interactive computer-based games without manipulating a mouse (Figure 2). The training program was adjusted automatically and continuously according to each participant's level of performance.

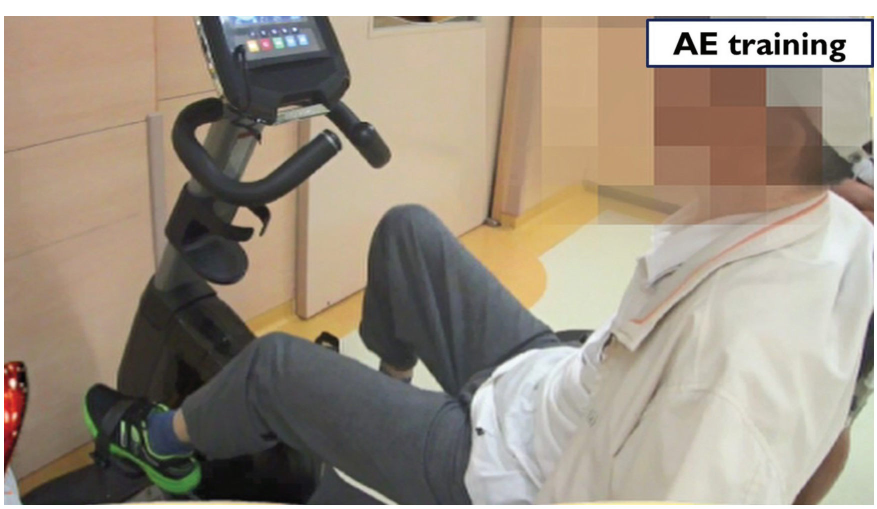

Figure 1. Aerobic exercise training (AE).

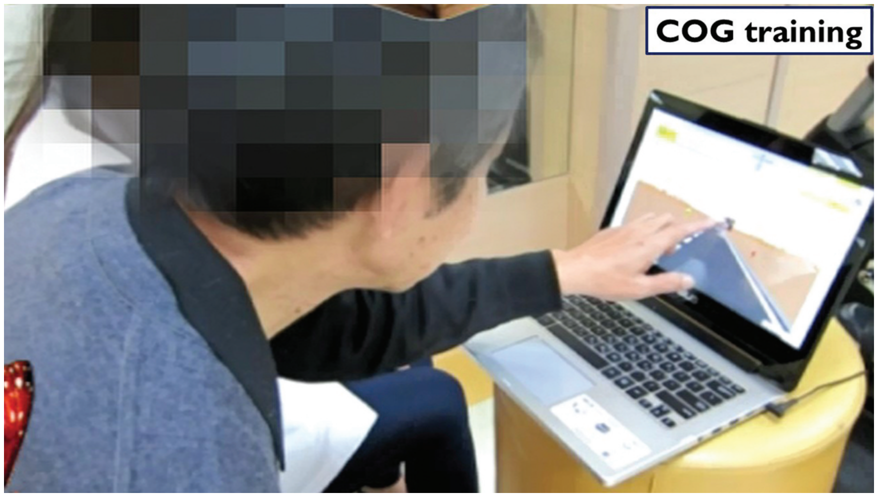

Figure 2. Cognitive training (COG).

Each cognitive intervention session was of 60 minutes.

SEQ training

The participants in the SEQ group underwent aerobic exercise training for 30 minutes, followed by 30 minutes of computer-based cognitive training (Figure 3). The aerobic exercise training was conducted using the progressive resistive stationary bicycle as in the AE group with the same training principle. The participants performed 3 minutes of warm-up, followed by 25 minutes of aerobic resistive exercise, and ended with 2 minutes of cool-down. After the aerobic exercise training, the participants took part in 30 minutes of computer-based cognitive training as in the COG group. The principles of the training program were the same as those of the cognitive training group. The SEQ program was also adjusted automatically and continuously according to each participant's level of performance.

Outcome assessment

Cognitive and functional assessments were measured at baseline and at the end of the intervention at 12 weeks. The evaluator for the assessments was blinded to the group allocation.

Figure 3. Sequential combination of aerobic exercise and cognitive training (SEQ).

Primary outcome measures

Primary outcome measures were cognitive functions as assessed by MoCA, Wechsler Memory Scale-Third Edition (WMS-III), and the Stroop Color and Word Test.[17,18] MoCA is a screening instrument for mild cognitive dysfunction, and it assesses six different cognitive domains, including short-term memory; visuospatial abilities; executive functions; attention, concentration, and working memory; language; and orientation to time and place. The WMS-III is a standardized and reliable neuropsychological examination tool designed to evaluate visuospatial and memory functions. Face recognition, verbal paired associates, word lists, and spatial span of the WMS-III subtests were used to assess the immediate, delayed, and working memory.[18] The Stroop Color and Word Test was used to assess the abilities of selective attention, inhibition, and executive function.[19]

Secondary outcome measures

Secondary measures included physical functions, ADL, instrumental AD (IADL), quality of life (QOL), and social participation. Physical functions were measured by the 6-Minute Walk Test (6MWT) and the Timed Up and Go test (TUG).[20,21] The 6MWT measures the maximum distance walked over 6 minutes and is a common tool to assess the endurance and mobility levels. The TUG is a performance-based measure of functional mobility by asking the participants to stand up from a chair, walk 3 m, return to the chair, and sit down. The Functional Independence Measure (FIM) and Lawton Instrumental Activities of Daily Living Scale (Lawton IADL) were used to evaluate ADLs and IADL.[22,23] The Lawton IADL is an instrument used to assess independent living skills such as the ability to use telephone or managing own medications. The QOL was assessed with the Stroke Impact Scale (SIS) 3.0.[24] The SIS is a self-report questionnaire that evaluates disability and health-related QOL, such as emotion, communication, memory and thinking, and social role function after stroke. The participant's level of social participation was measured using the Community Integration Questionnaire (CIQ).[25] CIQ is a brief, reliable measure of an individual's level of integration into the home and community.

Statistical analyses

All statistical analyses were performed using PASW Statistics 18.0 software (SPSS Inc., Chicago, IL, USA). The normality of the data was checked using the Shapiro–Wilks test and non-normally distributed variables were rank transformed to achieve normality, followed by analysis with parametric tests. The baseline characteristics of the participants were compared using chi-square (χ^2) tests and the Fisher's exact test. A 2 times (pre vs. post) × 3 groups (AE vs. COG vs. SEQ) mixed ANOVA with repeated measures on the time factor was conducted for all the outcome measures. If a significant interaction was found, the least significant differences post hoc analyses were conducted. We used the Huynh–Feldt correction factor when the data violated the sphericity assumption (Mauchly test, $p < .05$). The effect size (partial eta squared, η2) was calculated to determine the group difference for each outcome measure. The effect size greater than 0.138 is considered to be a large effect; between 0.138 and 0.059 is a moderate effect, and between 0.01 and 0.059 is a small effect.[26] For all tests, the statistical significance was set at $p < .05$.

Results

Baseline characteristics

Initially, 84 stroke survivors were selected and referred from the department, 28 of them were ineligible. Specifically, 28 interested stroke survivors were excluded due to several reasons: cognitive intact (n = 7), severe cognitive decline (n = 13), currently participating in another study (n = 3), and refused to participate (n = 5). Overall, 56 stroke survivors with cognitive impairment were randomized and divided into the SEQ (n = 20), AE (n = 18), and COG (n = 18) groups and were used in the final analysis. Figure 4 shows the CONSORT flow diagram. No significant differences in the baseline demographic characteristics were detected among the groups ($p > .05$ for all; Table 1).

Primary outcome measures

The mixed-factor analysis of variance revealed a significant group × time interactions for MoCA ($F_{2,53} = 4.05$, $p = .023$), Word List II ($F_{2,53} = 3.99$, $p = .024$), and Word List IA delayed ($F_{2,53} = 4.60$, p

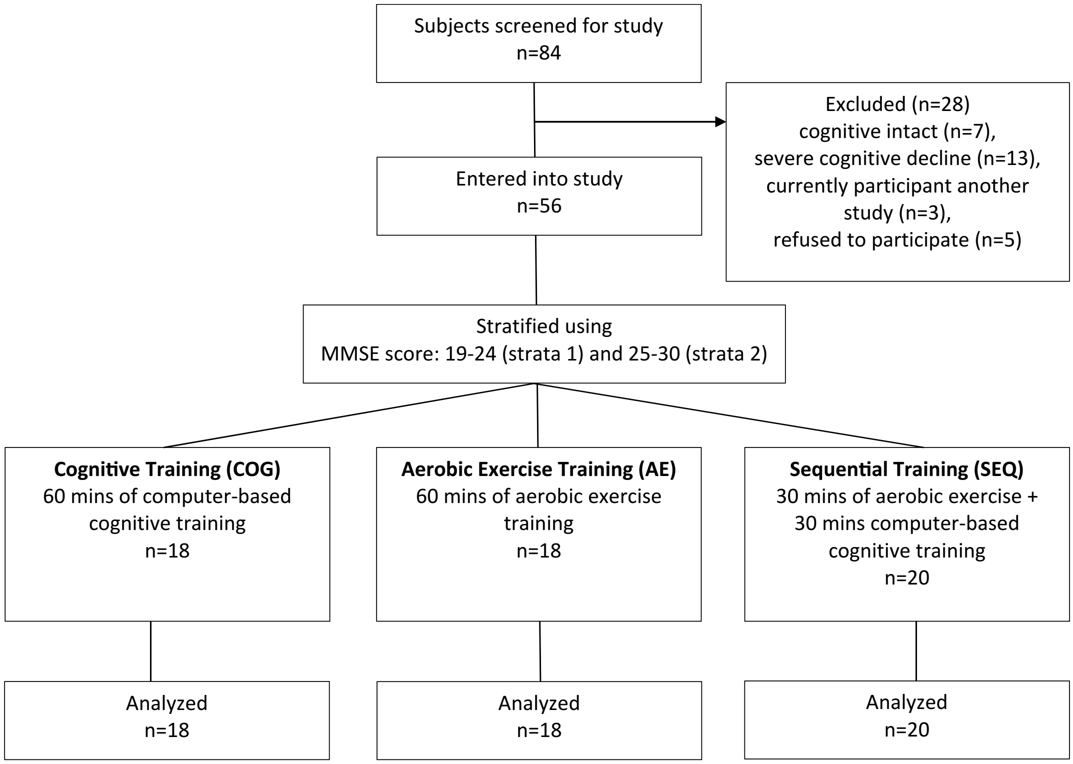

Figure 4. CONSORT diagram.

= .014; Table 2). To examine this interaction, the least significant difference post hoc analysis showed that after the training, the SEQ group improved to a significantly higher amount in the MoCA compared with the AE (p = .019) and COG groups (p = .017), but no between-group difference was found for the AE and COG groups (p > .05). Similar results were also shown for Word List II that the SEQ group significantly improved compared with the AE (p = .019) and the COG groups (p = .024). Finally, for the Word List IA delayed, the SEQ and COG groups both performed better than the AE group (SEQ: p = .010; COG: p = .018).

Table 1. Demographic and clinical features of the participants.

Variables	SEQ (n = 20)	AE (n = 18)	COG (n = 18)	*p*-value
Age (year)	53.05 ± 14.53	57.36 ± 12.17	60.17 ± 12.13	0.372
Time after stroke (months)	54.75 ± 55.24	34.28 ± 31.54	49.83 ± 45.43	0.504
Gender				0.649
Male	12 (60)	13 (72.22)	13 (72.22)	
Female	8 (40)	5 (27.78)	5 (27.78)	
Side of brain lesion				0.632
Right	7 (35)	9 (50)	7 (38.89)	
Left	13 (65)	9 (50)	11 (61.11)	
Stroke subtype				0.293
Ischemic	8 (40)	12 (66.67)	8 (44.44)	
Hemorrhagic	12 (60)	5 (27.78)	10 (55.56)	
Unknown		1 (5.56)		
NIHSS score	5.05 ± 4.72	4.5 ± 3.33	4.61 ± 3.05	0.989
MMSE score	25.15 ± 3.83	25.33 ± 3.60	25.50 ± 2.81	0.887
Education (year)	11.38 ± 3.73	11.33 ± 3.71	11.83 ± 4.63	0.735

NOTE. Values are mean ± SD or n (%)
Abbreviations: NIHSS: National Institute of Health Stroke Scale, MMSE: Mini-Mental State Examination, SEQ: Sequential combination of aerobic exercise and cognitive training, AE: Aerobic exercise training, COG: Cognitive training, SD: standard deviation.

Secondary outcome measures

For the secondary measures in TUG, 6MWT, FIM, Lawton-IADL, CIQ, and SIS, none of the comparisons within and between the groups were significant (Table 3).

Discussion

Comparisons of the three groups showed that the sequential combination training resulted in the largest improvement of the general cognitive function evaluated by MoCA compared to the single type of training. These results partially support our hypotheses that combined aerobic exercise and cognitive training engender larger cognitive effects than cognitive and exercise training alone. Positive

Table 2. Primary outcome measures.

	Pre-training			Post-training			Mixed ANOVA	
	SEQ (n = 20)	**AE** (n = 18)	**COG** (n = 18)	**SEQ** (n = 20)	**AE** (n = 18)	**COG** (n = 18)	*p*-value of group × time	Partial η^2
MoCA	19.15 ± 4.90	19.39 ± 4.33	20.28 ± 5.34	24.25 ± 4.49	21.72 ± 5.64	22.57 ± 6.02	**0.023**	0.132
WMS								
Faces	31.75 ± 6.14	29.44 ± 5.41	31.67 ± 4.60	33.05 ± 4.59	31.22 ± 5.87	33.43 ± 4.46	0.939	0.002
Verbal paired associates	7.05 ± 4.91	8.53 ± 6.94	10.13 ± 8.35	−1.95 ± 6.68	−2.76 ± 9.53	−6.38 ± 10.61	0.218	0.056
Word List IA	22.58 ± 5.77	20.17 ± 8.69	21.22 ± 10.97	27.79 ± 6.54	22.11 ± 9.29	26.07 ± 10.08	0.175	0.064
Word List IB	4.05 ± 2.33	3.22 ± 2.16	3.00 ± 1.71	4.04 ± 1.63	3.22 ± 1.90	4.14 ± 2.00	0.218	0.074
Word List II (%)	48.80 ± 34.09	48.59 ± 34.51	56.71 ± 40.68	63.44 ± 33.11	41.22 ± 30.74	50.17 ± 33.92	**0.024**	0.131
Word List IA delayed	4.11 ± 3.08	4.17 ± 2.96	4.44 ± 3.55	5.95 ± 3.28	3.89 ± 2.63	6.07 ± 3.60	**0.014**	0.148
Spatial Span	12.60 ± 4.63	12.67 ± 2.50	13.39 ± 3.55	14.50 ± 3.76	13.06 ± 2.86	12.86 ± 3.91	0.068	0.096
Stroop								
Congruence accuracy (No.)	36.53 ± 19.04	44.29 ± 15.76	52.94 ± 18.41	41.79 ± 20.10	47.82 ± 16.54	52.26 ± 17.02	0.219	0.056
Incongruence accuracy (No.)	13.75 ± 10.60	11.94 ± 8.81	18.72 ± 10.26	14.60 ± 11.34	14.83 ± 10.14	20.36 ± 10.53	0.413	0.033

Values are mean ± SD. Values in bold are statistically significant.
Abbreviations: MoCA: Montreal Cognitive Assessment, WMS: Wechsler Memory Scale, SEQ: Sequential combination of aerobic exercise and cognitive training, AE: Aerobic exercise training, COG: Cognitive training.

Table 3. Secondary outcome measures.

	Pre-training			Post-training			Mixed ANOVA	
	SEQ (n = 20)	AE (n = 18)	COG (n = 18)	SEQ (n = 20)	AE (n = 18)	COG (n = 18)	*p*-value of group × time	Partial η^2
TUG (second)	34.94 ± 25.57	36.84 ± 25.72	51.28 ± 52.82	37.37 ± 34.57	38.68 ± 30.21	53.93 ± 47.59	0.986	0.001
6MWT (meter)	168.60 ± 95.24	152.36 ± 103.85	145.90 ± 105.52	193.21 ± 112.84	168.87 ± 107.67	150.14 ± 102.45	0.416	0.033
FIM	103.80 ± 18.03	109.39 ± 11.21	103.44 ± 18.10	104.00 ± 19.84	111.94 ± 7.98	102.38 ± 18.12	0.211	0.057
Lawton-IADL	22.25 ± 5.37	24.22 ± 4.66	21.67 ± 5.69	22.65 ± 7.56	24.33 ± 4.61	23.45 ± 5.90	0.468	0.028
CIQ	7.95 ± 4.00	8.06 ± 2.85	8.53 ± 4.98	9.65 ± 3.59	9.54 ± 3.99	9.79 ± 4.77	0.884	0.005
SIS (%)	62.10 ± 15.38	69.44 ± 13.98	62.02 ± 14.24	64.43 ± 21.73	70.98 ± 20.78	65.12 ± 12.89	0.938	0.002

Values are mean ± SD.
Abbreviations: TUG: Timed Up and Go test, 6MWT: 6-Minute Walk Test, FIM: Functional Independence Measure, CIQ: Community Integration Questionnaire, SIS: Stroke Impact Scale, SEQ: Sequential combination of aerobic exercise and cognitive training, AE: Aerobic exercise training, COG: Cognitive training.

effects of improving general cognitive function after stroke in favor of combined treatment were observed. However, no significant group difference was shown in physical functions and other health-related outcomes.

Aerobic exercise has been shown to enhance post-stroke cognitive performance in the Trail-Making test, Serial Addition test, and Stroop test.[14,27,28] The findings of our study are partially consistent with the results of prior research in supporting that aerobic exercise not only improves general cognitive function (e.g. MoCA) but also optimizes memory function measured by four subtests of WMS-III. Aerobic exercise may lead to upregulation of neurotrophic and vascular growth factors, such as brain-derived neurotrophic factor.[29] We speculated that AE does not involve the practice of specific cognitive tasks and that improving results on these specific cognitive tests might not be easy. Yet, AE improved brain blood flow and oxygen perfusion, which may evoke cortical activation of the frontal lobe and possibly promote improvements in general cognitive function.[30]

The superior performance in the MoCA and WMS-III subtests in the SEQ group may have resulted because of the fact that the aerobic exercise before cognitive training increases the arousal level and consolidates memory, which may benefit subsequent memory retrieval and cognitive task performance.[10,11] Our study demonstrates that the combination of aerobic exercise and computerized cognitive training has synergistic effects that improve the cognitive function of stroke patients. It may be that the combined training provided a more varied and richer sensory and motor experience that may promote neural plasticity such as synaptogenesis or strengthen synaptic activities.[31]

An important difference between our study and previous work is that we investigated a variety of outcomes related to stroke patient's ADL, QOL, and social participation. Although sequential training may result in improvements in general and specific cognitive domains, the training effects are insufficient transferring to everyday functional ADL, QOL, and social participation. In accordance with this, a previous systematic review suggested that cognitive improvement seems to remain confined to trained cognitive functions rather than generalizing to other daily living skills.[32] However, another recent work conducted by Oh and Jung found that a 4-week cognitive training program is beneficial in restoring cognitive function and improving ADL in stroke patients.[33] Cognitive and physical disabilities resulting from a stroke can possibly lead to activity limitations and participation restrictions.[34] Further study is needed to investigate the transfer effect of the sequential combination training on the daily functions and participation aspects of the stroke survivors.

Our recent study investigated the psychometric and clinimetric properties of MoCA in stroke survivors, and the minimal clinically important difference (MCID) values were estimated to be 1.22 and 2.15 according to the anchor-based and distribution-based methods, respectively.[35] Stroke survivors who achieve the threshold value may demonstrate a clinically important change. In the current study, the difference in comparing pre- to post-training are as follows: SEQ (from 19.15 to 24.25, difference = 5.1), AE (from 19.39 to 21.72, difference = 2.33), and COG (from 20.28 to 22.57, difference = 2.29). Three training groups have exceeded MCID based on both anchor-based and distribution-based methods, indicating that the participants in each training group perceived the training protocols as beneficial and meaningful.[35]

Some limitations of our study warrant consideration. First, the SEQ group received a half dose of the active ingredient of aerobic exercise and cognitive training compared with the COG and AE training groups. However, previous research has provided little evidence of the individually optimal intensity of aerobic exercise or computerized cognitive training of the combined program. The findings of this study might provide the groundwork for future investigations to explore the ideal training parameters. Second, the sample size was relatively small. Follow-up studies using a larger sample for the study are needed to validate the findings. Additional research is needed to investigate patient characteristics that influence intervention effectiveness.

Lastly, the training effects were measured immediately after the training. Whether the benefits of sequential training can be retained over time is unknown. The larger the sample population would allow, a more generalized interpretation of the results.

Conclusions

The findings may provide evidence for the potential synergistic intervention in cognitive function in stroke survivors. Future studies investigating the transfer effects and the optimal training parameters of the sequential training with a large sample size will be beneficial to those stroke survivors with mild cognitive impairment.

Acknowledgments

We thank and acknowledge the support from the research team and the staff from our recruiting sites who contributed to setting up and running this study.

Funding

This study was supported by Chang Gung Memorial Hospital [CMRPD1F0411-413, CMRPD1E0283]; the Ministry of Science and Technology [MOST106-2314-B-182-024-MY3]; Healthy Aging Research Center, Chang Gung University from the Featured Areas Research Center Program within the framework of the Higher Education Sprout Project by the Ministry of Education (MOE) [EMRPD1H0391] in Taiwan.

ORCID

Ting-Ting Yeh http://orcid.org/0000-0001-7341-6793

References

1. Gillespie D, Campbell F. Effect of stroke on family carers and family relationships. *Nurs Stand*. 2011;9 (2):39–46. doi:10.7748/ns.26.2.39.s51.
2. Claesson L, Lindén T, Skoog I, et al. Cognitive impairment after stroke - impact on activities of daily living and costs of care for elderly people. The Göteborg 70+ stroke study. *Cerebrovasc Dis*. 2005;19(2):102–109. doi:10.1159/000082787.
3. Pollock A, St George B, Fenton M, et al. Top 10 research priorities relating to life after stroke-consensus from

stroke survivors, caregivers, and health professionals. *Int J Stroke*. 2014;9(3):313–320. doi:10.1111/j.1747-4949.2012.00942.x.

4. Van de Ven RM, Murre JM, Veltman DJ, et al. Computer-based cognitive training for executive functions after stroke: a systematic review. *Front Hum Neurosci*. 2016;10:150. doi:10.3389/fnhum.2016.00150.
5. Cumming TB, Tyedin K, Churilov L, et al. The effect of physical activity on cognitive function after stroke: a systematic review. *Int Psychogeriatr*. 2012;24(4):557–567. doi:10.1017/S1041610211001980.
6. Zheng G, Zhou W, Xia R, et al. Aerobic exercises for cognition rehabilitation following stroke: a systematic review. *J Stroke Cerebrovasc Dis*. 2016;25(11):2780–2789. doi:10.1016/j.jstrokecerebrovasdis.2016.07.035.
7. Schneider N, Yvon C. A review of multidomain interventions to support healthy cognitive ageing. *J Nutr Health Aging*. 2013;17(3):252–257. doi:10.1007/s12603-012-0402-8.
8. Oswald WD, Gunzelmann T, Rupprecht R, et al. Differential effects of single versus combined cognitive and physical training with older adults: the SimA study in a 5-year perspective. *Eur J Ageing*. 2006;3(4):179–192. doi:10.1007/s10433-006-0035-z.
9. Liu-Ambrose T, Eng JJ. Exercise training and recreational activities to promote executive functions in chronic stroke: a proof-of-concept study. *J Stroke Cerebrovasc Dis*. 2015;24(1):130–137. doi:10.1016/j.jstrokecerebrovasdis.2014.08.012.
10. Labban J, Etnier J. Effects of acute exercise on long-term memory. *Res Q Exerc Sport*. 2011;82(4):712–721. doi:10.1080/02701367.2011.10599808.
11. Coles K, Tomporowski PD. Effects of acute exercise on executive processing, short-term and long-term memory. *J Sports Sci*. 2008;26(3):333–344. doi:10.1080/02640410701591417.
12. Yeh T, Wu C, Hsieh Y, et al. Synergistic effects of aerobic exercise and cognitive training on cognition, physiological markers, daily function, and quality of life in stroke survivors with cognitive decline: study protocol for a randomized controlled trial. *Trials*. 2017;18. doi:10.1186/s13063-017-2153-7.
13. Kim GY, Han MR, Lee HG. Effect of dual-task rehabilitative training on cognitive and motor function of stroke patients. *J Phys Ther Sci*. 2014;26:1–6. doi:10.1589/jpts.26.1.
14. Quaney BM, Boyd LA, McDowd JM, et al. Aerobic exercise improves cognition and motor function poststroke. *Neurorehabil Neural Repair*. 2009;23(9):879–885. doi:10.1177/1545968309338193.
15. Tanaka H, Monahan KD, Seals DR. Age-predicted maximal heart rate revisited. *J Am Coll Cardiol*. 2001;37(1):153–156. doi:10.1016/S0735-1097(00)01054-8.
16. Lee YY, Wu CY, Teng CH, et al. Evolving methods to combine cognitive and physical training for individuals with mild cognitive impairment: study protocol for a randomized controlled study. *Trials*. 2016;10(1):526. doi:10.1186/s13063-016-1650-4.
17. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695–699. doi:10.1111/j.1532-5415.2005.53221.x.
18. Wechsler D.*Wechsler Memory Scale–Third Edition Manual*. TX editor. San Antonio: The Psychological Corporation; 1997.
19. Stroop JR. Studies of interference in serial verbal reactions. *J Exp Psychol*. 1935;18:643–662. doi:10.1037/h0054651.
20. Enright PL. The six-minute walk test. *Respir Care*. 2003;48:783–785.
21. Shumway-Cook A, Brauer S, Woollacott M. Predicting the probability for falls in community-dwelling older adults using the timed up & go test. *Phys Ther*. 2000;80(9):896–903. doi:10.1093/ptj/80.9.896.
22. Granger CV, Hamilton BB, Zielezny M, et al. Advances in functional assessment in medical rehabilitation. *Top Geriatr Rehabil*. 1986;1:59–74. doi:10.1097/00013614-198604000-00007.
23. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist*. 1969;9(3):179–186. doi:10.1093/geront/9.3_Part_1.179.
24. Carod-Artal FJ, Coral LF, Trizotto DS, et al. The stroke impact scale 3.0: evaluation of acceptability, reliability, and validity of the Brazilian version. *Stroke*. 2008;39(9):2477–2484. doi:10.1161/STROKEAHA.107.513671.
25. Sander AM, Fuchs K, High WM, et al. The community integration questionnaire revisited: an assessment of factor structure and validity. *Arch Phys Med Rehabil*. 1999;80(10):1303–1308. doi:10.1016/S0003-9993(99)90034-5.
26. Portney MP, Watkins LG. *Power and Sample Size. Foundations of Clinical Research: Applications to Practice*. 3rd ed. NJ: Pearson/Prentice Hall; 2009.
27. Ploughman M, McCarthy J, Bossé M, et al. Does treadmill exercise improve performance of cognitive or upper-extremity tasks in people with chronic stroke? A randomized cross-over trial. *Arch Phys Med Rehabil*. 2008;89(11):2041–2047. doi:10.1016/j.apmr.2008.05.017.
28. Pyöriä O, Talvitie U, Nyrkkö H, et al. The effect of two physiotherapy approaches on physical and cognitive functions and independent coping at home in stroke rehabilitation. A preliminary follow-up study. *Disabil Rehabil*. 2007;29(6):503–511. doi:10.1080/09638280600902497.
29. Tari AR, Norevik CS, Scrimgeour NR, et al. Are the neuroprotective effects of exercise training systemically mediated? Prog. *Cardiovasc Dis*. 2019;62:94–101. doi:10.1016/j.pcad.2019.02.003.
30. Li L, Men W-W, Chang Y-K, et al. Acute aerobic exercise increases cortical activity during working memory: a

functional MRI study in female college students. *PLoS One*. 2014;9(6):e99222. doi:10.1371/journal.pone.0099222.

31. Donnezan LC, Perrot A, Belleville S, et al. Effects of simultaneous aerobic and cognitive training on executive functions, cardiovascular fitness and functional abilities in older adults with mild cognitive impairment. *Ment Health Phys Act*. 2018;15:78–87. doi:10.1016/j.mhpa.2018.06.001.
32. Lauenroth A, Ioannidis AE, Teichmann B. Influence of combined physical and cognitive training on cognition: a systematic review. *BMC Geriatr*. 2016;16:141. doi:10.1186/s12877-016-0315-1.
33. Oh EY, Jung MS. Effects of a cognitive training program on cognitive function and activities of daily living in patients with acute ischemic stroke. *J Korean Acad Nurs*. 2017;47(1):1–13. doi:10.4040/jkan.2017.47.1.1.
34. deSouza FHN, daSilva Filho EM, Cezarino LG, et al. Social Participation as a goal of the post-stroke rehabilitation program: a literature review. *Manual Ther Posturology Rehabil J*. 2017;15:503.
35. Wu CY, Hung SJ, Lin KC, et al. Responsiveness, minimal clinically important difference, and validity of the MoCA in stroke rehabilitation. *Occup Ther Int*. 2019;2019:2517658. doi:10.1155/2019/2517658.