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Effects and mechanism of the HECT study (hybrid exercise-cognitive trainings) in mild ischemic stroke with cognitive decline: fMRI for brain plasticity, biomarker and behavioral analysis

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ABSTRACT

Purpose: Cognitive decline after stroke is highly associated with functional disability. Empirical evidence shows that exercise combined cognitive training may induce neuroplastic changes that modulate cognitive function. However, it is unclear whether hybridized exercise-cognitive training can facilitate cortical activity and physiological outcome measures and further influence on the cognitive function after stroke. This study will investigate the effects of two hybridized exercise-cognitive trainings on brain plasticity, physiological biomarkers and behavioral outcomes in stroke survivors with cognitive decline.

Methods and significance: This study is a single-blind randomized controlled trial. A target sample size of 75 participants is needed to obtain a statistical power of 95% with a significance level of 5%. Stroke survivors with mild cognitive decline will be stratified by Mini-Mental State Examination scores and then randomized 1:1:1 to sequential exercise-cognitive training, dual-task exercise-cognitive training or control groups. All groups will undergo training 60 min/day, 3 days/week, for a total of 12 weeks. The primary outcome is the resting-state functional connectivity and neural activation in the frontal, parietal and occipital lobes in functional magnetic resonance imaging. Secondary outcomes include physiological biomarkers, cognitive functions, physical function, daily functions and quality of life. This study may differentiate the effects of two hybridized trainings on cognitive function and health-related conditions and detect appropriate neurological and physiological indices to predict training effects. This study capitalizes on the groundwork for a non-pharmacological intervention of cognitive decline after stroke.

1. Introduction

Advances in stroke management and organized post-acute care lead to lower stroke mortality. In contrast to the great emphasis on recovery in physical function, post-stroke cognitive decline has largely been ignored. Approximately 20%–60% of stroke survivors have cognitive decline three months after stroke [1]. Patients with cognitive decline may experience difficulties learning motor tasks and thus reduce the intervention effects.

Current evidence indicates that targeted cognitive rehabilitation after stroke–including cognitive or aerobic exercise training provided potential benefits to enhance cognitive function. Computerized cognitive training is a common technique to restore executive functioning after a brain injury or other neurological event [3]. The mechanism of cognitive training might be associated with increased cortical activation and functional connectivity (FC) between the hippocampus and the frontal and the parietal cortices [4]. Exercise, on the other hand, can improve physical functions such as increased muscle mass, strength,

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Table 1
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Stroke occurring at least 6 months prior to enrollment	Unstable medical history (e.g., recent myocardial infarction) that might limit participation
Age range from 20 to 80 years	Concomitant with other neurological disorders (e.g., Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis)
MMSE score < 28 or MoCA < 25	Current participation in another interventional trial
Able to follow the study instruction	Pregnant woman
Adequate cardiopulmonary function to perform physical activity	Any contraindication to MRI (metallic implants, claustrophobia, seizure, pacemakers, et al.)
Able to walk with or without assistive devices	MMSE score < 19

MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment.

power, endurance and mobility level [5]. The physiological adjustments after exercise involve glycemic control, oxidative stress modulation, and lipoprotein metabolism modification [6–8]. Efficacy research on both cognitive and exercise has shown to up-regulate neurotrophic and vascular growth factors, such as the brain-derived neurotrophic factor (BDNF) and may indirectly facilitate general cognitive function [9,10].

Combining exercise and cognitive training could have synergistic or complementary effects on cognition at both the neurobiological and behavioral levels [11,12]. Sequential training is combining exercise and cognitive training sequentially. Aerobic exercise before cognitive training may increase arousal level and enhance memory consolidation which may benefit the following memory retrieval and cognitive task performance [11,13]. Winter et al. [14] observed that intense exercise led to elevated levels of BDNF, which is known to promote long-term potentiation, synaptic connection, and neural plasticity. Law et al. [12] suggested that exercise sessions delivered before the cognitive training session preparing the brain for the compensatory recruitment process in the subsequent cognitive training sessions.

Dual-task training is when the participant performs exercise and cognitive tasks simultaneously. Dual-task training is more cognitively demanding because it involves additional cognitive processing to integrate and coordinate two tasks at the same time [15]. Kim and colleagues [2] investigated the effect of dual-task training on cognition in patients with chronic stroke and found that compared with single-task training, four weeks of dual-task training led to improvements in the walking abilities and executive functions measured by the Stroop test. The enhanced cognitive function was maintained at two weeks follow-up. Many activities of daily life involve the simultaneous performance of multiple tasks concurrently challenging motor and cognitive functions. Stroke survivors with cognitive decline has been significantly associated with daily life functional dependence and reduced quality of life [16]. To investigate the generalizability of dual-task training effects to real world and functional outcomes is of utmost importance.

The evidence for the hybridized exercise-cognitive training either sequentially or concurrently (i.e., in a dual-task paradigm) for individuals with stroke is limited. We are primarily interested in the changes in cortical activity before and after hybridized exercise-cognitive training in patients with stroke. The secondary outcomes include the physiological biomarkers (e.g., BDNF), cognitive functions, physical functions, daily functions and quality of life. We hypothesize that the exercise-cognitive hybridized trainings could potentially facilitate a wide range of functions. These outcome measures that accompany hybridized exercise-cognitive training in stroke survivors have not been evaluated. Whether the hybridized exercise-cognitive training can improve the activities of daily living (ADL) and quality of life (QOL) needs to be determined given that the fundamental goal of rehabilitation is to improve everyday functioning. Resolving in a randomized controlled trial study the effects of two hybrid exercise-cognitive trainings (HECT) on brain plasticity, physiological biomarkers, and behavioral outcomes is therefore of great importance.

2. Methods

2.1. Design

The study is an interventional, single-blind randomized controlled trial that will be performed in Taiwan. The protocol has been approved by the Institutional Review Board (approval number: KMUHIRB-F(II)-20170040) of Kaohsiung Medical University Chung-Ho Memorial Hospital, Kaohsiung, Taiwan. The protocol is registered in clinical.trials.gov as NCT03230253. All patients will provide written informed consent.

2.2. Patient population

The inclusion criteria will be (1) stroke occurring at least 6 months prior to enrollment; (2) age range from 20 to 80 years; (3) Mini-Mental State Examination (MMSE) score < 28 or Montreal Cognitive Assessment (MoCA) < 25; (4) able to follow the study instruction; and (5) adequate cardiopulmonary function to perform physical activity; (6) able to walk with or without assistive devices. Exclusion criteria will be (1) MMSE score < 19; (2) unstable medical history, such as recent myocardial infarction, that might limit participation; (3) concomitant with other neurological disorders (e.g., Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis); and (4) currently involve in other research projects; (5) Pregnant woman. Potential participants will be also excluded if they have any contraindication to fMRI scanning, including claustrophobia, seizures, the presence of pacemaker, metal elements (e.g., steel pins or plates) inside the body or in the eyes, and excessive obesity (see Table 1).

2.3. Randomization

Randomization will be performed using the web-based data entry system (i.e., Research Randomizer) by a research assistant. Randomization will be stratified by the baseline cognitive function using the MMSE (low: 19–24; high: 25–27). Participants will be randomly 1:1:1 to sequential exercise-cognitive training (SEQ), dual-task exercise-cognitive training (DUAL) or control group according to a predefined table.

2.4. Interventions

All training will be conducted 60 min per day, 3 days a week, for a total of 12 weeks. Vital signs and the Borg Perceived Exertion Scale [17] will be monitored and recorded.

2.4.1. SEQ training

The participant in the SEQ group will first undergo physical exercise training for 30 min followed by 30 min of cognitive-based intervention. We will use a stationary bicycle to provide resistive aerobic training during the physical exercise training [18]. The target heart rate during the aerobic period will be 40–70% of maximal heart rate calculated as (208 − 0.7 × age) [19]. The exercise intensity will be progressed as the

participants improve their performance throughout practice. Vital signs and the Borg Perceived Exertion Scale [17] will be monitored and recorded for each session. During the 30 min physical exercise, the participants will first perform three minutes of warm-up followed by 25 min of aerobic resistive exercise, and end with two minutes of cool-down.

Following the physical exercise, the participants will take part in 30 min of computerized cognitive-based intervention using BrainHQ (Posit Science Inc., San Francisco, CA, USA), a commercialized cognitive training program. The BrainHQ will be used to train participants a variety of cognitive functions. We aim to target the abilities of visuospatial processing, attention, memory, and executive function [20]. Therefore, the participants will practice the *Hawk Eye*, *Divided Attention, Eye for Detail, Scene Crasher, Mental Maps, and Optic Flow* in BrainHQ. The tasks will become more difficult as the participants progress in their cognitive abilities.

2.4.2. DUAL training

The participant in the DUAL group will be instructed to perform the resistive aerobic exercise while performing cognitive tasks simultaneously. The resistive aerobic exercise for the DUAL group will be performed on the stationary bicycle as described in the SEQ group. While exercising on the bicycle, the participants will be given cognitive tasks to perform using the BrainHQ cognitive training program. Since dual-task training involves the integration of two tasks [21], it will be more cognitively demanding than performing single task. To avoid potential frustration of the participants, easier versions of the cognitive tasks will be used in the beginning. The cognitive tasks will be designed based on similar principles as the tasks practiced with BrainHQ which will involve trainings in visuospatial processing, attention, memory, and executive functions. The exercise intensity and the difficulty of the cognitive tasks will increase as the participants improve their dual-task performance.

2.4.3. Control training

The control participants will receive 60 min of health-related rehabilitation programs which involve non-aerobic physical exercise (e.g., muscle stretching, range of motion exercises, relaxation techniques) and unstructured cognitive related rehabilitation programs (e.g., watch health-related videos or read newspapers or magazines and then answer the content-related questions raised by the therapist).

2.5. Outcome measures

At the baseline assessment, the National Institutes of Health Stroke Scale (NIHSS), Fugl-Meyer Assessment (FMA), and MMSE will be used to determine the disease severity of the participants. Primary outcome of changes in resting-state FC as well as the neural activation while performing the cognitive tasks in the frontal, parietal and occipital lobes will be assessed by fMRI. Secondary outcomes include the physiological biomarkers (e.g., BDNF), cognitive functions (visuospatial, attention, memory, and executive abilities), physical functions, daily functions and quality of life. The fMRI data, physiological biomarkers and behavioral outcome measures will be evaluated before, immediately after and 6 months after the intervention programs.

2.5.1. Primary outcome and experimental procedure

Resting-state functional connectivity (FC) and neural activation in the frontal, parietal and occipital lobes will be assessed by functional magnetic resonance imaging (fMRI) before, immediately after, and 6 months after the intervention. The participants will be scanned during quiet resting to obtain the changes of resting-state FC. Participants will also be tested individually in the laboratory and conduct two cognitive tasks: (1) Wisconsin Card Sorting Task (WCST) and (2) N-back working memory task, in two separate sessions, with a seven-day interval. The cognitive task performance will be analyzed.

(1) *Wisconsin Card Sorting Task (WCST).* The WCST is designed to assess abstract reasoning ability and cognitive flexibility in response to changing environmental contingencies (set-shifting) [22]. A computerized version of the WCST will be administered using stimulus presentation software (Media Control Function; Digivox, Montreal, Canada). Before the scanning session, the participants will be fully trained on the task. During scanning, the computer display will be projected onto a mirror in the MRI scanner. Throughout this task, four fixed reference cards will be presented in a row on the top of the screen, displaying one red triangle, two green stars, three yellow crosses, and four blue circles, respectively. On each trial, a new test card will be presented in the middle of the screen below the reference cards. Participants will be instructed to match the choice card with one of the four reference cards following one of two possible task rules, namely, either “sort by color” or “sort by shape” [23]. Participants will be told that the task rule will change at random and that they will have to shift tasks frequently. Before the target onset, a tonal cue informs whether to switch or repeat the previous task. Tonal switch and repeat cues occurred with 50% probability each, and they signal each of the two tasks also with equal mean probability.

(2) *N-back working memory task.* The N-back task is a continuous performance task that is commonly used as an assessment in cognitive neuroscience to measure the working memory. A modified N-back task will be programmed using MATLAB 7.0 software (The MathWorks, Natick, MA, USA). The N-back task consists of a sequence of stimuli, in which participants are asked to identify whether the current stimulus matches the stimulus from N steps earlier in the sequence, and the cognitive load is elevated with the operating number of N. In the present study, the non-word symbols (e.g., circle, square or triangle) will be presented in the 0-back, 1-back, and 2-back conditions. In the 1-back condition, the target trial is a symbol stimulus that is identical to the symbol that immediately preceded it (i.e., the symbol presented one trial back), whereas in the 2-back condition, the target trial is a symbol stimulus that is identical to the symbol presented two positions before it (i.e., the symbol presented two trials back). Each block condition includes 18 trials (6 target trials and 12 non-target trials) in random order. Each letter stimulus will be displayed on the screen for 2000 ms [24].

2.5.2. fMRI data acquisition and scanning protocol

MRI data will be collected using a 3-T Signa (GE) MR scanner equipped with an 8-channel phased-array head coil at Chang Gung Memorial Hospital, Kaohsiung, Taiwan. Each participant will be asked to remain still, keep their eyes closed, and think of nothing in particular. A foam pillow will be used to restrict head movement, and the earplugs will be provided to reduce noise interference. We will adopt previously validated MRI imaging protocols and acquire whole-brain functional images using echo-planar imaging (EPI) to measure blood oxygenation level dependent (BOLD) signal changes related to cognitive tasks. In addition, high-resolution T2 contrast images that are in alignment with the EPI images for later co-registration to 3D T1 high-resolution structural brain images will be acquired using the MPRAGE sequences. A T2-weighted gradient-echo image with BOLD contrast (TR, 3000 msec; TE, 50 msec; FA, 90°; voxel size, $3 \times 3.5 \times 3.5\,mm^3$) will be used subsequently. Functional images will be obtained to measure BOLD signal changes related to the cognitive tasks by using an EPI sequence, with the following scan parameters: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle (FA) = 90°, slice thickness = 3.75 mm, field of view (FOV) = $192 \times 192\,mm^2$, and voxel size = $3.0 \times 3.0 \times 3.75\,mm^3$, with 243 brain volumes with 32 axial slices.[3]

2.5.3. fMRI data processing

fMRI data analysis will be conducted using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/), implemented in MATLAB

7.0 software (The MathWorks, Natick, MA, USA). The first four volumes of each functional session will be discarded to allow for T1 equilibration effects. The images will be preprocessed with slice-timing and motion correction, and normalized to Montreal Neurological Institute (MNI) template. Images were then smoothed with an isotropic 6-mm full-width half-maximum 3-dimensional Gaussian kernel. A 2-stage general linear model will be used to examine the effect sizes of each condition and to compare them at the group level. Individual data will be analyzed using a fixed-effects model, and the group data will be analyzed using a random-effects model.

To identify brain regions involved in the relative effects of post-training from pre-training as well as the long-term effects from the follow-up assessment, the whole-brain analysis (including within-group and between-group comparisons) will be performed. For within-group analyzes, the main effect of treatment will be computed for each participant by contrasting the cognitive task trials of the post-treatment session with the pre-treatment session and follow-up session with the post-treatment session. In addition, between-group comparisons will be calculated to reveal brain areas that are significantly more activated in one group compared with the other as well as the interactions among groups by way of contrast. A statistical threshold of $p = 0.05$, false discovery rate (FDR) corrected, and an extent threshold of $k > 10$ voxels will be used for whole-brain analysis.

In addition to the whole-brain approach, we will use the peak results from the pre-training session as regions-of-interest (ROI) in a hypothesis-driven approach to assess training-induced changes in activity and correlations with behavioral performance. The ROIs of the template involves the posterior cingulate cortex (PCC), prefrontal cortex and inferior parietal lobe (IPL), which are assumed to be the core areas associated with the cognitive functions. The neural connectivity in the default mode network (DMN) which included precuneus, PCC, IPL, medial temporal lobes, medial frontal cortex, and anterior cingulate cortex will be evaluated. Lastly, the hippocampal FC will be targeted as another important neural marker associated with the memory function.

2.6. Secondary outcomes

Secondary outcomes include the physiological biomarkers, cognitive functions (visuospatial, attention, memory, and executive abilities), physical functions, daily functions and quality of life will be assessed before, immediately after, and 6 months after the intervention.

2.6.1. Biomarkers

The cognitive and physical related biomarkers will be collected. In particular, the level of BDNF will be a biomarker following cognitive rehabilitation, whereas the antioxidative marker, blood glucose indicator and plasma lipid levels will also be evaluated as physical-related factors. Blood samples will be collected at baseline, immediately after and six months after the intervention programs. Venous blood will be collected into sampling tubes and centrifuged at 2000 × g for 15 min. Serum will be then harvested, aliquoted, and stored at −80 °C until analysis. The automated ferric-reducing ability of plasma (FRAP) assay will be implemented to measure the antioxidative marker.

2.6.1.1. BDNF level. Serum BDNF will be quantified using an enzyme-linked immunosorbent assay (Human BDNF Quantikine Immunoassay, DBD00, R&D Systems) according to the manufacturer's instructions. This sandwich ELISA is set in order to measure natural and recombinant human mature BDNF in serum and plasma. All assays will be performed on F-bottom 96-well plates (Nunc, Wiesbaden, Germany).

2.6.1.2. Antioxidative marker. Antioxidative markers will be used to reflect the changes on oxidative stress. In particular, we will be analyzing the total antioxidant capacity (TAC).

2.6.1.3. Glucose indicator. HbA1C level will be tested to investigate the relationships between blood glucose level and aerobic exercise.

2.6.1.4. Plasma lipid level. The cholesterol ratio (total cholesterol divided by high-density lipid) will be evaluated to reflect the lipid level in the blood.

2.6.2. Behavioral outcomes

Behavioral outcome contains three parts: (1) the cognitive functions, (2) the physical functions, and (3) the daily functions which included ADLs and quality of life. The behavioral assessment will be administered in two separate days to prevent from fatigue due to a variety of evaluations. The behavioral data will be collected at baseline, immediately after and six months after the intervention programs.

2.6.2.1. Cognitive functions. To have a comprehensive assessment of cognitive functions before and after intervention, we will evaluate the general cognition (e.g., Montreal Cognitive Assessment) and subtypes of cognitive function (e.g., visuospatial, attention, memory and executive function).

2.6.2.1.1. Montreal Cognitive Assessment (MoCA). The MoCA will be used to assess general cognitive functions. It examines several cognitive domains with a total score of 30. The MoCA has been shown to be a feasible tool to evaluate the global cognitive function in a large population of patients with stroke [25]. The reliability and validity have been established to be good to excellent for patients with cerebrovascular diseases [26].

2.6.2.1.2. Wechsler Memory Scale – Third edition (WMS–III). The WMS–III is a standardized and reliable neuropsychological examination tool designed to evaluate visuospatial and memory functions [27]. We will use the WMS–III subtests, including Faces Recognition, Verbal Paired Associates, Word Lists, and Spatial Span to assess the immediate, delayed, and working memory tests [28]. The Faces Recognition test involves 24 pictures of human faces. The participants will be required to look through the faces one by one, and later recognize those faces. For the Verbal Paired Associates test, the instructor will read out eight-word pairs for the participant to memorize. The participants will be asked to respond to the appropriate word that matches the test word. In the Word Lists test, the instructor will read out 12 words in a list and the participants will need to repeat as many words as they could immediately and 25–35 min after. As for the Spatial Span test, the instructor will point to spatially located blocks in a sequential order; the participants will then touch the blocks either in the same sequential order or in a reversed order. The test-retest reliability of these subtests has been established to be moderate in community-dwelling adults [29].

2.6.2.1.3. Wechsler adult Intelligence Scale – Third edition (WAIS–III). The WAIS–III is developed to measure an individual's intelligence level. It includes tests that evaluate cognitive functions in verbal comprehension, working memory, perceptual organization, and processing speed [30]. The subtests that we will use are the Digit Symbol-Coding and Matrix Reasoning tests. The Digit Symbol-Coding test consists of 9 digit-symbol pairs and the participants will be asked to write down the corresponding symbols for the given digits on the test sheet as accurately and as fast as possible. As for the Matrix Reasoning test, the participants will need to logically solve missing puzzles within given matrixes. The test result of the Matrix Reasoning test indicates a general intelligence level because it entails the abilities of visual-spatial reasoning, abstract reasoning, visual organization, and visuospatial information processing [31].

2.6.2.1.4. Useful Field of View (UFOV). The UFOV assessment is a computer-based visual test containing three subtests: visuomotor processing speed, divided attention, and selective attention [32]. The UFOV is the visual area over which information can be extracted from a brief glance without eye or head movements. The UFOV has been shown to have good test-retest reliability and validity to assess patients with stroke [33].

2.6.2.1.5. Stroop Color-Word test. The Stroop Color-Word assesses the abilities of selective attention, inhibition and executive function. The participants will be tested under congruent and incongruent conditions. In the congruent condition, the participant will name the color ink of a word which is consistent with the written color name; whereas in the incongruent condition the participant will name the color ink differs from the written color name. In both conditions, the number of colors correctly named within 45 s will be measured and the performance in the congruent condition will be compared with the incongruent condition [34].

2.6.2.1.6. Dual-task test. The dual-task test evaluates the ability to shift attention between one task and another. Participants will perform the box and block test (BBT) while doing secondary cognitive tasks while sitting. Participants will perform BBT by affected and less affected hand. Two cognitive secondary tasks will be performed by the participants: (1) arithmetic task: participants will be asked to perform serial subtractions by 3 starting from 100 or random two-digit numbers [35]; (2) tone discrimination task: participants will be presented a number of low and high-pitched tones and they will calculate and remember the number of high-pitched tones during the trial. Both cognitive task performances will be recorded and the results will be compared to single cognitive task performance. In addition to the BBT, participants will perform both secondary cognitive tasks while walking.

2.6.2.2. Physical functions. Physical function assessments include balance, muscle endurance and strength, mobility level, as well as changes in health-related physical activity and motor impairment level.

2.6.2.2.1. Timed up and go (TUG). The TUG assesses the dynamic balance ability and mobility. Decreased lower-limb muscle strength has been shown to positively correlate to balance impairments in stroke survivors [36,37]. Our physical exercise training includes resistive aerobic exercise, which can potentially improve lower extremity muscle strength and balance control. The participants will be required to stand up from a chair, walk 3 meters, turn around, walk back to the chair, and sit down. The time to complete the TUG test has been shown to be a good indicator to detect potential fallers in frail elderly [38]. The test-retest reliability of TUG on individuals with stroke was excellent [39].

2.6.2.2.2. Six-minute walk test (6MWT). The 6MWT measures the maximum distance walked over 6 min, which assess the endurance and mobility level of the participants. The participants could rest as needed during the course of the test. The test-retest reliability and responsiveness has been established to be high for patients with chronic stroke [40].

2.6.2.2.3. Mobility level. Accelerometers will be used to provide an objective measure of the amount of arm movements in real-life situations. The participants will be asked to wear an Actigraphy activity monitor (ActiGraph, Shalimar, FL, USA) on both wrists for 3 consecutive days before and after training to measure the number of moves each minute, and the average counts of move per minute. The participants will be required to wear the device during the day except for doing water-based activities, such as bathing or swimming. Data recorded by the actigraphy will be analyzed with the MAHUFFE software (http://www.mrc-epid.cam.ac.uk/). The use of actigraphy to measure arm use and physical activity has been established for patients with stroke [41].

2.6.2.2.4. International Physical activity Questionnaires (IPAQ). The IPAQ is an international measure of health-related physical activity. The short form version of the Chinese IPAQ will be used to assess changes in physical activity before and after the intervention. The reliability and validity of IPAQ have been established in 12 countries [42,43].

2.6.2.2.5. Fugl-Meyer Assessment (FMA). The 33-item upper limb subscale of the FMA will be used to assess motor impairments. Items are scored on a three-point ordinal scale (0 = cannot perform, 1 = performs partially, 2 = performs fully), with a total of score of 66. Proximal shoulder/elbow and distal hand/wrist subscores will be calculated. The reliability, validity, responsiveness, and clinically important differences of the FMA have been well established in stroke patients [44,45].

2.6.2.2.6. Rivermead Mobility Index (RMI). The RMI evaluates the participant's bed mobility, postural transfers and walking ability. It contains a 15-item scale which includes 14 questions and one direct observation, with a total of score of 15. The RMI has been shown to have excellent correlations with Functional Independence Measure (FIM) and the Barthel Index [46].

2.6.2.2.7. Lower extremity muscle strength. We will evaluate isometric knee flexors and extensors muscle strength using handheld dynamometer. The participant will be seated upright in a chair with back support, the knee will be placed in 90-degree flexion and the evaluator will stabilize the thing to eliminate synergistic movements. Participants will be asked to perform a maximal isometric contraction of knee flexion and extension with affected and less affected side. We will record the mean value of 3 attempts.

2.6.2.3. Daily functions and quality of life. The FIM and Lawton will be used to evaluate ADLs, and quality of life will be assessed with SIS, EQ-5D, and CB scale.

2.6.2.3.1. Functional Independence Measure (FIM). The FIM assesses the dependence level of individuals with stroke to perform 18 activities (13 motor and five cognitive tasks) in daily living. The score ranges from 18 to 126 and higher scores demonstrate greater independent participation in daily activities [47]. The FIM has good inter-rater reliability and validity [48].

2.6.2.3.2. Lawton Instrumental activities of Daily Living Scale (Lawton IADL). The Lawton IADL scale assesses independent living skills, such as shopping or managing finances [49]. It has often been shown that the ability to perform IADL declines before basic ADL; hence, evaluate IADLs may help clinicians to identify early deterioration in physical and/or cognitive functions. The Lawton IADL scale evaluates 8 activities with a score range from 0 to 8 (higher indicate better function). The inter-rater reliability and validity of the Lawton IADL have been established to be moderate to high for community-dwelling older adults [49,50].

2.6.2.3.3. Stroke Impact Scale (SIS). The SIS 3.0 will be used to evaluate health-related quality of life for patients with stroke. The SIS assesses eight domains (strength, hand function, ADL/IADL, mobility, communication, emotion, memory and thinking, and participation/role function) with 59 test items. The participants rate each item according to their perceived difficulty to accomplish the task during the past week. The psychometric properties of SIS in individuals with chronic stroke have been well established [51].

2.6.2.3.4. Caregiver Burden (CB) scale. CB scale evaluates the burden of the primary caregiver of the participants. Lessening the burden of caregivers after the intervention may significantly improve the quality of life for patients with stroke and their family. The CB scale measures factors related to general strain, isolation, disappointment, emotional involvement, and environment of the caregivers. The CB scale for caregivers of stroke patients showed moderate to good test-retest reliability and construct validity [52].

2.6.2.3.5. EuroQoL (EQ)-5D questionnaire. The quality of life will be assessed by the EQ-5D questionnaire which comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has three levels: no problems, some problems, extreme problems. The score has been shown to be reliable and valid [53].

2.7. Data monitoring committee

A Data Monitoring Committee (DMC) comprising clinicians and one statistician will oversee the study. They will review and evaluate the accumulated data periodically; patient safety and treatment efficacy

will also be monitored. The DMC may recommend terminating the study for safety concerns.

2.8. Sample size estimates

To date, there is no published research investigating the effects of hybrid training combining aerobic exercise and cognitive training on cognitive functions in stroke populations. The sample size estimate was based on published work [2,54] which had a similar target stroke population and behavioral outcome measures. We calculated the effect size (Cohen's d) of the outcome measure from Lin et al. [54]: Wechsler Memory Scale as well as the effect sizes of two outcome measures from Kim et al. [2]: (1) Time up and go test and (2) Stroop test. We then transformed the Cohen's d into effect sizes f. G*Power software [55] was used to estimate the number of participants needed for this project. The parameters set in the G*Power software were based on our study design. Considering a significance level of 5%, a power of 95%, and an effect size f = 0.25, the required number of patients per group was estimated to be 20. Allowing for 20% attrition at the 6-month follow-up, we plan to recruit 75 participants (25 for each group).

2.9. Statistical analyses

The intention-to-treat analysis will be used for efficacy. Continuous-scale outcomes will initially be assessed for normality and log-transformed where appropriate. We will use the analysis of variance (ANOVA) and χ^2 to analyze differences in baseline characteristics and baseline outcome measures among the groups. To determine the intervention effect for the three groups at three-time points (baseline, post-intervention, and follow-up), repeated measures ANOVA will be performed. Tukey's post hoc test will be carried out if a group × time interaction or a main effect is observed. A statistical significant level will be set at 0.05 for all comparisons. Besides the *p*-values, the effect size (partial eta squared, η^2) will be calculated to determine 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 [56]. In addition, the correlations among neural activity, FC, physiological biomarkers and neuropsychological performance will be analyzed using a linear regression model at $p < 0.05$ and an extent threshold of 10 voxels. All data analysis will be performed with PASW Statistics 18.0 software (SPSS Inc., Chicago, IL).

3. Discussion

Cognitive deficits after stroke are highly associated with functional disability, institutionalization rate, and mortality, and have risk for developing dementia. Treatment to reserve cognitive ability is emergent and attention has shifted toward this less visible cognitive impairment over the recent decades. There is no consensus about pharmacological interventions [57], and it is not highly recommended the use of only medicines for cognitive decline after stroke. Accordingly, it is important to structure non-pharmacological interventions to increase or reserve patients' cognitive capacity. This project represents endeavor toward this possibility.

Physical function and behavioral improvements resulting from exercise or cognitive training were established to a certain degree in certain populations. Despite abundant studies have used fMRI to monitor the changes of neural activities in different brain regions during stroke recovery, the changes in the neural activities that underlie the behavioral improvements are not well understood. Functional neuroimaging such as fMRI has been suggested to be an important source of information about the effects of cognition-related trainings. Neuroimaging can also determine the intervention mechanisms at the cognitive and neural levels, possibly showing changes in FC and the patterns of brain activation.

Sporadic researches on underlying the neural mechanisms associated with cognitive training following stroke were reported recently. For example, Yang and colleagues [58] examined the effects of integrated cognitive therapy that combined computer-based cognitive rehabilitation and cholinesterase inhibitors on cognitive function in ischemic stroke. Participants were scanned at baseline and after the integrated cognitive therapy. Using the resting-state fMRI, stroke patients showed increased hippocampal FC mainly in the prefrontal gyrus and the DMN after treatment. Their results also found the increased FC was correlated with the improved cognitive performance. Similarly, another study with ten weeks computer-assisted cognitive training in stroke patients also demonstrated an increased hippocampal FC in frontal and left parietal lobe compared with patients without intervention [54]. Moreover, this increased FC was correlated with the improvement in memory test by Wechsler Memory Scale and executive function by Trail Making Test [54]. Both studies highlighted the possible contribution of computer-based cognitive rehabilitation in modulating neural networks in stroke patients, as reflecting on the increased FC and improvement of cognitive performance.

Although resting-state fMRI can elucidate the brain's functional connections by determining temporal synchrony between brain regions, whether the training-induced changes in the neural activity associated with cognitive training remains unexplored. Event-related fMRI with BOLD contrast technique might be better in representing functionality of brain regions at least in normal subjects performing various cognitive tasks [59]. To the best of our knowledge, only one case study investigated the patterns of neural activation after a course of auditory working memory training using event-related fMRI. Leung and colleagues [60] found that the stroke patient improved the N-back task performance throughout the training and demonstrated improvement in cognitive abilities including attention, working memory and short-term memory after one-month training. Functional imaging showed a pattern of decreased neural activation in the frontoparietal attention network post-training which suggested a decreased compensation for functional deficits and may be linked to cognitive function recovery. This preliminary work provided promising evidence that auditory working memory training could enhance neural efficiency in performing the working memory task. The changes in neural activities might be specific to the training.

On the other hand, training-induced brain plasticity associated with physical exercise in healthy young adults has been examined. A recent study used the fMRI to examine the effect of acute aerobic exercise on working memory task-evoked brain activity in healthy young subjects [24]. They found that single bout of 20 min moderate intensity aerobic exercise induced brain activation in the right middle prefrontal gyrus, the right lingual gyrus, and the left fusiform gyrus as well as deactivations in the anterior cingulate cortexes, the left inferior frontal gyrus, and the right paracentral lobule. The authors suggest that these specific brain cortexes play vital roles in the alteration of executive function induced by acute exercise.

To sum up, beginning evidence suggests that cognitive and physical exercise training may positively induce neuroplastic changes in stroke patients with cognitive impairment or healthy adults. However, results of such training for patients with brain lesions are scarce. No study used the task-evoked neural activity in various areas, network circuit, and resting-state FC to investigate neural changes after hybrid exercise-cognitive trainings and their mechanisms. There is also no study trying to disentangle the possible differences in brain plasticity after different types of hybrid exercise-cognitive trainings. In addition, including an active control group and examining the long-term follow-up effect for hybrid exercise-cognitive trainings need to be explored as well.

The HECT trial is to our knowledge the first randomized controlled trial to assess the effects of two hybridized interventions on brain plasticity, physiological biomarkers and behavioral outcomes in stroke survivors. This study will ascertain the clinical significance of changes in cognitive function by measuring the behavioral outcomes and

quantifying the relationship among neural connectivity, physiological biomarkers, and behavioral outcomes. The fMRI measurement at three-time points will illustrate the time course of the neural mechanisms associated with cognitive training in stroke survivors over six months of hybrid interventions for cognitive recovery.

Given the limited efficacy of current cognitive interventions, as the growing interest in recovery from stroke sequelae, developing integrated and novel training strategies for cognitive impairment is of vital importance. Cognitive treatments and recovery have been listed among the top 10 research priorities after stroke [61]. While cognitive and aerobic exercise training are well evidenced for improving cognitive function, limited efficacy of cognitive interventions for stroke survivors are established. This clinical trial will launch two novel hybrid cognitive trainings and compare the effects in stroke survivors with mild cognitive decline. This trial will also determine whether cognitive function enhancement is associated with changes in brain structure and physiological biomarkers. Our findings will indicate whether the hybrid interventions are feasible and effective for stroke survivors with mild cognitive decline. The findings might inform clinicians how neurobiological change and adaptive modulation occur after specific hybrid training and which type of hybrid therapy engenders specific treatment effects at the specific behavioral performance. Investigation of relations among neural connectivity/activation, physiological biomarkers and behavioral outcomes might underscore the possible neural connectivity/activity patterns relating to or predicting the effects of specific hybrid training. Such examination also explores the brain-behavior relations and detects appropriate patients responsive to specific hybrid training in terms of neurological and/or physiological indices.

Trial registration

ClinicalTrials.gov: NCT03230253.

Competing interests

The authors declare that they have no competing interests.

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