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ORIGINAL ARTICLE

Using virtual reality-based training to improve cognitive function, instrumental activities of daily living and neural efficiency in older adults with mild cognitive impairment

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ABSTRACT

BACKGROUND: A combination of physical and cognitive training appears to be the effective intervention to improve cognitive function in older adults with mild cognitive impairment (MCI). Computing technology such as virtual reality (VR) may have the potential to assist rehabilitation in shaping brain health. However, little is known about the potential of VR-based physical and cognitive training designed as an intervention for cognition and brain activation in elderly patients with MCI. Moreover, whether a VR program designed around functional tasks can improve their instrumental activities of daily living (IADL) requires further investigation.
AIM: This study investigated the effects of 12 weeks of VR-based physical and cognitive training on cognitive function, brain activation and IADL and compared the VR intervention with combined physical and cognitive training.
DESIGN: A single-blinded randomized controlled trial.
SETTING: Communities and day care centers in Taipei, Taiwan.
POPULATION: Older adults with mild cognitive impairment.
METHODS: Thirty-four community-dwelling older adults with MCI were randomized into either a VR-based physical and cognitive training (VR) group or a combined physical and cognitive training (CPC) group for 36 sessions over 12 weeks. Participants were assessed for their cognitive function (global cognition, executive function and verbal memory) and IADL at pre- and postintervention. Changes in prefrontal cortex activation during the global cognition test were also captured by functional near-infrared spectroscopy (NIRS) to identify the potential mediating pathway of the intervention.
RESULTS: Both groups showed improved executive function and verbal memory (immediate recall). However, only the VR group showed significant improvements in global cognition ($P<0.001$), verbal memory (delayed recall, $P=0.002$), and IADL ($P<0.001$) after the intervention. The group × time interaction effects further demonstrated that IADL were more significantly improved with VR training than with CPC training ($P=0.006$). The hemodynamic data revealed decreased activation in prefrontal areas after training ($P=0.0015$), indicative of increased neural efficiency, in the VR-trained subjects.
CONCLUSIONS: VR-based physical and cognitive training improves cognitive function, IADL and neural efficiency in older adults with MCI.
CLINICAL REHABILITATION IMPACT: VR training could be implemented for older adults with MCI.

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KEY WORDS: Cognitive dysfunction; Aged; Virtual reality; Cognition; Activities of daily living; Near-infrared spectroscopy.

According to the Alzheimer's Association, approximately 15% to 20% of older adults aged 65 and over experience mild cognitive impairment (MCI),[1], which represents a transient state of cognitive decline seen in normal aging and in those diagnosed with Alzheimer's disease (AD).[2] Instrumental activities of daily living (IADL) include activities of complex and intentional cognitive processes, such as shopping and managing money, and are critical for one to live independently in a community.[3] Researchers have found that older adults with MCI had lower IADL scores than their healthy counterparts.[4] In addition, compared to older adults with normal IADL, older adults with both MCI and IADL deficits are more likely to develop dementia[5]. Given the subsequent risk of MCI for developing dementia, interventions targeting MCI have great potential to preserve cognitive function as well as to maintain intact IADL.

In a previous review study, cognitive training led to significant improvements in memory, executive function, processing speed, attention, fluid intelligence, and subjective evaluation of cognitive functioning among older adults with MCI.[6] Cognitive training not only improved cognitive functioning but also benefited functional performance that is fundamental to performing IADL.[7, 8] Similar to cognitive training, physical exercise has also been one of the interventions. Öhman *et al.* found that aerobic exercise, weight training, balance training, and tai chi were among the typical components of physical training programs for enhancing cognitive function in older adults with MCI, especially in the domains of executive functioning, attention and delayed recall.[9] Recently, mounting evidence also pointed out that combining physical and cognitive training may strengthen the intervention effects on cognitive function in older adults with MCI.[10-13] For example, Barnes *et al.* stated that older adults with MCI who received both aerobic exercise and mental activity training showed improvements in global cognitive function.[14] Whereas the positive effects of combined physical and cognitive training on cognitive functions have been robust in the literature, most studies did not find that these training effects successfully transferred to IADL improvement.[12]

Information and computer technology (ICT) has become a popular approach in assessing cognitive functioning because it provides an ecologically valid treatment. A systematic review of ICT-based cognitive or physical training has shown the positive effects of these technology applications on attention, visual memory and verbal memory, as well as executive function of older adults with MCI.[15] Virtual reality (VR), one of the most advanced ICT technologies, provides an immersive, intuitive, motivating, interactive and multisensory feedback context in which participants can practice customized activities of daily living in the virtual environment that conventional rehabilitative interventions could not offer.[16, 17] However, most articles about VR training are either physical or cognitive training.[16] Studies on the effects of combining both physical and cognitive training in the VR context are lacking. Moreover, these studies have not been intended for improving IADL. Given the fact that IADL require high demands in physical activity and cognitive resources, particularly executive functioning and memory, the IADL-based cognitive and physical training programs in the VR context may more likely transfer from the intervention effect to their actual IADL. However, evidence for these innovative interventions requires further investigation.

Brain imaging techniques provide a more in-depth understanding of cognitive aging and the physiological mechanisms responsible for intervention efficacy. Near-infrared spectroscopy (NIRS), an innovative neuroimaging technique, measures hemodynamic changes during brain activation. In comparison with fMRI, the advantages of NIRS include lower costs, portability, lower susceptibility to movement artifacts, and a high temporal sampling rate. Compared to cognitively preserved counterparts, those with MCI showed higher activation in the dorsolateral prefrontal cortex during a memory task. This increased activity may reflect a compensatory mechanism enabling them to perform normally due to malfunctioning memory networks in subjects with MCI.[18] However, previous findings have shown mixed patterns of post-training brain activation in subjects with MCI. Using fMRI, Belleville *et al.* found increased activation after memory training in the frontal, temporal and parietal areas in subjects with MCI.[19] However, Vermeij *et al.* did not find any working memory training-related changes in prefrontal activation.[20] In addition, studies applying VR as an intervention strategy for brain activation in older adults with MCI are still lacking.

Thus, the present study aimed at exploring the effects of VR-based physical and cognitive training on cognitive functions, brain activation, and IADL, as well as comparing the VR intervention to a traditional combined physical and cognitive training program.

Materials and methods

Participants

Participants were recruited from communities and day care centers in Taipei, Taiwan. All participants met the following inclusion criteria: 1) aged 65 years old and above; 2) able to walk more than 10 meters without walking aids; 3) had an MMSE (Mini-Mental State Examination) score greater than or equal to 24 and a Montreal Cognitive Assessment (MoCA) score lower than 26;[21] 4) had self-reported memory complaints; 5) had the ability to perform ADLs. The exclusion criteria were: 1) a diagnosis of dementia; 2) a history of malignant tumors; 3) the presence of unstable neurological or orthopedic disease that would have interfered with participation in the study; 4) an education level less than six years (elementary school). The study protocol was approved by the Institutional Human Research Ethics Committee of National Yang-Ming University and has been registered at www.clinicaltrials.in.th (TCTR20181001001 on October 1st, 2018). All participants provided signed informed consent before participation. G*power 3.0 was used to determine the sample size needed for the present study. Before starting the study, we could not find any articles using the same intervention (virtual reality) and the same primary outcome (MOCA). Therefore, our sample size calculation was conducted by Hwang *et al.*,[22] which showed that the virtual reality training group had a greater improvement in the Visual Span Test after intervention. Based on the calculated effect size for the Visual Span Test (Cohen's d=0.357), we estimated the sample size for the current study to be 17 participants in each group.

Study design

This study was a single-blinded (assessor) randomized controlled trial. Recruitment and screening were performed between October 2018 and January 2019. Recruitments were conducted in communities and day care centers in Taipei city by three assessors (physiotherapists). Screening evaluations were performed during the same periods by the same assessors to confirm the MCI patients. Randomization was performed after eligible subjects signed the informed consent. Participants meeting the criteria were randomly assigned to either the VR group or the CPC group *via* a sealed envelope. Participants in the VR group participated in a 60-minute, VR-based physical and cognitive training session each visit, three times a week for 12 weeks. Those in the CPC group participated in combined physical and cognitive training program for 60 minutes each visit, three times a week for 12 weeks. Exercise training was conducted by an experienced physical therapist for both the VR and CPC groups. In each community, small group training (3-4 people in a group) was conducted instead of large group training (more than 10 people in a group) because we wanted to control the quality of intervention. The outcomes were measured at baseline and after completing 36 sessions by the same assessor who was always blinded to the group assignments.

Intervention

Combined physical and cognitive training (CPC) group

The physical training program was based on exercise programs suggested for elderly populations from the American College of Sports Medicine[23] and consisted of resistance exercises, aerobic exercise, and balance exercises. During resistance exercise, Therabands were used on both upper and lower extremities. During aerobic exercise, a sequence of whole-body activities was performed, including stepping exercises in seated and standing positions, stepping on and off of a stool, and standing up from and sitting in a chair, to allow participants to achieve 50-75% of the maximal heart rate (HR_{max} = 220 − age). Perceived exertion was obtained using Borg's scale (scores ranging from 6 to 20, where 6 means "no exertion at all" and 20 means "maximal exertion"), and the ideal observed effort was a score of 13 to 14 ("somewhat hard"). Balance exercises included static and dynamic balance training. Functional tasks that can enhance motor performance and simulate tasks of activity of daily living were also integrated into our physical training programs, for example, stair climbing, obstacle crossing, walking forward, backward and sideways, turning, rising from a chair, and squatting when reaching for objects. The exercise progressions included adding more weights and increasing the number of repetitions during resistance exercise, increasing the difficulty of exercise, such as increasing the height of the stool during aerobic exercise, increasing the forward/sideward reaching distance during the balance exercise, and holding the squatting position for a longer duration during the squatting exercise.

Cognitive training was simultaneously introduced during the exercise. A sample combined physical and cognitive exercise could include the following: walking and turning around while reciting poems, crossing obstacles of various heights while enumerating animals or flowers, strengthening lower extremity muscles while practicing math calculations, stepping in place with one or both hands drawing circles in the air in a clockwise or counterclockwise manner, drawing a clock with one hand in the air while practicing weight shifting, and looking for prefix/roots of a Chinese character while performing the sit-to-stand task.

VR-based physical and cognitive training (VR) group

In each session, participants participated in VR-based physical training for 40 minutes and cognitive training for 20 minutes. Details on the physical and cognitive programs in this group are as follows.

VR-based physical exercise program

The Kinect system (Microsoft Corporation, Redmond, WA, USA) was used for capturing and tracking changes in limb segment motions with infrared light. This system also created a full-body 3D virtual map. Our VR-based physical training programs were developed by Tano and Long-Good. Participants imitated the virtual characters and adjusted their movements in real time according to the instantaneous visual and auditory feedback. Exercises included simplified 24-form Yang-style tai chi, resistance exercises, aerobic exercises and functionally oriented tasks such as window cleaning, goldfish scooping, obstacle crossing, stair climbing and walking designed to improve upper and lower extremities, balance, stability, muscle strength, and endurance.

VR-based cognitive training program

The VIVE system developed by the HTC company was used for the present study. The station was placed on the diagonal of the activity space with a maximum sensing space of 4×3 meters. The participants wore VR glasses on their heads and had motor controllers in both hands during the training. Some VR games were invented by our laboratory, while others were derived from the commercially available software "Job Simulator" developed by Owlchemy Labs. The design concept of the VR games was based on actual IADL, such as shopping, food preparation, handling finances, and transportation. The participants were guided by verbal instructions and asked to memorize the instructions and certain spatial characteristics. Four games used in the current study are described as follows (Figure 1):

- take mass rapid transit (MRT): the game was designed to mimic the environment of a MRT station. Every MRT station was equipped with gates, ticket vending machines, and ATMs. Participants were asked to follow the standard procedure of metro transit (*e.g.*, find the designed station, gather an accurate amount of money based on the fare chart and obtain a ticket from a vending machine). A large red cross would show up as a notification if things were going wrong;
- looking for a store: in this game, participants were asked to find stores marked on a map. The search should be completed in three minutes. If the participants had not found the store in the first two minutes, there would be direction marks in red to guide the way for the participants;
- kitchen chef: the kitchen was equipped with kitchen appliances such as a flow table, gas stove, refrigerator, etc., and there were some cooking tools in the closet. The game began with an order of a particular dish. Step-by-step instructions were available to complete the meal. Participants were required to memorize the recipe and preparation steps. Simple dishes were introduced first, and if successfully completed, orders of more complex dishes, which took more ingredients and cooking utensils, would follow;
- convenience store clerk: the scene was a convenience store, including typical decorations (*e.g.*, checkout counters, cash registers, hot dog machines). The game began with a list of checkout items. Step-by-step instructions were also available for the participants to find these items, add to the shopping basket and complete the checkout. Similar to the kitchen chef game, not all the required tools were easily accessible.

Figure 1.—Schematic of the VR-based training program: A) taking the MRT; B) looking for a store; C) stepping and running; D) kitchen chef; E) convenience store clerk; F) tai chi; G) subject wearing VR glasses and performing VR tasks.

Outcome measures

Pre- and post-intervention outcome measures (neuropsychological tasks, functional status and brain activation) were measured by the same assessor (a physiotherapist with 6 years of experience), who was blinded to the group assignments.

Neuropsychological tasks

Global cognition

The MoCA was used to assess global cognition. The MoCA was divided into seven subcategories: visuospatial/executive, naming, memory, attention, language, abstraction, and orientation. The score ranged from 0 to 30, and a higher score indicated better global cognitive function. The MoCA has been used as an effective screening and evaluation instrument for cognitive impairments, including MCI and Alzheimer's disease.[24]

Executive function

The Executive Interview 25 (EXIT-25) was developed by Royall *et al.*[25] The EXIT-25 consisted of 25 items assessing a broad array of executive functions, including number/letter sequencing; word and design fluency; sentence repetition; thematic perception; memory with distraction; interference inhibition; grasp and snout reflexes; social habits; motor perseveration; finger-nose repetition; echopraxia; complex hand sequences; complex commands; counting and serial order reversal; and automatic, utilization, and imitation behaviors. The total score ranged from 0 to 50, with a possible score on each item of 0 to 2. A higher score indicated poorer executive function. The EXIT-25 has demonstrated a moderate internal consistency (α=0.66).[26]

Verbal memory

The Chinese version of the Verbal Learning Test (CVVLT) consisted of nine two-character nouns presented over four learning trials, with recall assessed immediately and after 10-minute delays. The examiner read the 9 words on the list aloud at one-second intervals in a fixed order over four learning trials. After each trial, the participant was asked to recall as many words as he/she could, in any order. After 10 minutes, the participant was again asked to recall the list. We calculated the total number of nouns correctly remembered to assess immediate recall and delayed recall. The CVVLT was translated from the original English version and has demonstrated sound psychometric properties.[27]

Functional status

Functional status was measured by the Lawton Instrumental Activities of Daily Living scale (IADL).[28] The IADL scale was composed of eight items to evaluate one's ability to perform tasks such as handling finances and preparing food. Responses to each of the eight items in the scale were coded as 0 (unable or partially able) or 1 (able). The summary score could range from 0 to 8, with higher scores indicating higher functional status and independence. The IADL scale can be used to differentially diagnose cognitively healthy aging and cognitive disorders in older adults. The reliability and validity have been established in Taiwan.[29]

Brain activation

A 16-channel NIRS device (OEG-16, Spectratech Inc., Yokohama, Japan) containing two types of infrared light (770 nm and 840 nm) was used to measure brain activation simultaneously with the assessment of the MoCA during the pre- and postintervention periods. A head module consisted of two rows of photodiodes with three sources and three detectors in each row and was attached to each participant's forehead using a headband to monitor the hemodynamics of the left, right and bilateral prefrontal cortex (PFC). The distance between the source and detector was 3 cm, which enabled hemodynamic measurements 2-3 cm beneath the skin. The detection optodes were placed 25-30 mm above the midpoint of the eyebrow at approximately FP1, and FP2 in the international 10/20 system standard for electroencephalography (Figure 2). Therefore, we defined CH4 and CH7 to represent the right PFC (EEG electrode site FP2) and CH10 and CH13 to represent the left

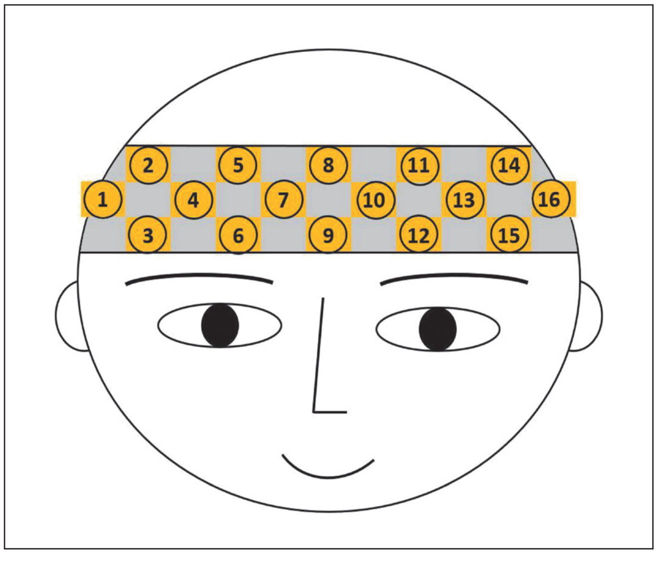

Figure 2.—Diagram of the functional near-infrared spectroscopy (NIRS) channels. The average of channels 4 and 7 represents the right prefrontal cortex. The average of channels 10 and 13 represents the left prefrontal cortex.

PFC (EEG electrode site FP1). The principle of NIRS is that near-infrared light penetrates the skull and is absorbed by the chromophores with different absorption spectra. The preprocessed signals were converted to concentration changes as oxygenated hemoglobin (HbO), deoxygenated hemoglobin (HbD), and total hemoglobin (HbT).[30, 31] The modified Beer-Lambert law was used for each source-detector channel.[32] HbO has been considered to be a robust and reproducible change in regional cerebral blood flow. Studies have shown that the fMRI BOLD response is more strongly correlated with HbO than with HbD, which may be due to the higher signal-to-noise ratio in HbO.[33] Therefore, only HbO-derived concentration changes (mM×mm) were used in the statistical analyses to evaluate brain activation.

Statistical analysis

We performed per-protocol analysis in this study. All statistical analyses were performed using SPSS v. 20.0 software (SPSS Inc. Chicago, IL, USA). Descriptive statistics were used to present the distribution of the variables as the mean and standard deviation or the number and proportion. Independent *t*-tests or Chi-square tests were used to detect the intergroup differences in baseline characteristics of the two groups. Two-way analysis of variance (ANOVA) with repeated measures was used to determine the effects of the VR and CPC interventions on cognitive function and gait performance. The model effects included groups (VR, CPC), time (pre, post), and their interaction. We compared differences between groups as well as the changes within a group from the pre- to postintervention assessments. Tukey's *post-hoc* tests were used for variables with group × time interaction effects. MATLAB software was used to analyze the NIRS data. The NIRS signals were bandpass filtered (a low-pass frequency of 0.01 Hz and a high-pass frequency of 0.1 Hz) to eliminate the effects of physiological spontaneous brain oscillations and to correct drift artifacts over the whole experimental session. We defined the baseline period as the 20 seconds prior to the onset of the task and the activation period as the 10 seconds before and 10 seconds after the peak HbO value during the MoCA task. Because our primary interest was to examine task-related changes in HbO, we defined the delta as the difference between the average HbO value of the activation period and the baseline period. The averages of the delta of CH4 and CH7 (right PFC), of CH10 and CH13 (left PFC), and of CH4, CH7, CH10, and CH13 (bilateral PFC) were used for statistical analyses of the within- and between-group comparisons. Statistical significance was set at P less than 0.05.

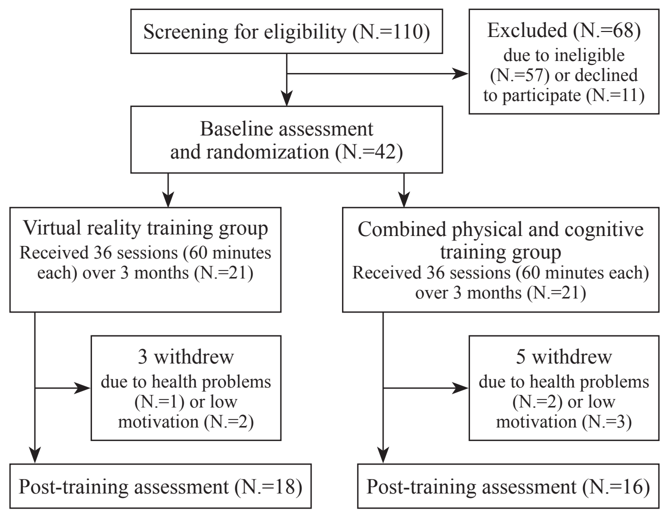

Figure 3.—Flow chart of this study.

Results

As shown in the flow chart in Figure 3, we screened 110 elderly individuals with the potential for mild cognitive impairment. A total of 68 elderly were excluded due to not meeting the inclusion criteria or declining to participate. We only retained the demographic data for the 42 eligible elderly individuals who signed the informed consent and were randomized. Of the enrolled individuals, 21 were randomly assigned to the VR group, and 21 were randomly assigned to the CPC group. In these 42 participants, three (one in the VR group and two in the CPC group) did not complete the study due to health problems unrelated to training and five (two in VR group and three in CPC group) dropped out due to low motivation. Therefore, a total of 34 participants (18 in the VR group and 16 in the CPC group) completed all the assessments, and their data were used in the final statistical analyses. None of the participants reported any adverse events.

The demographic characteristics of the participants are shown in Table I. There were no significant differences in the demographic parameters of the two groups. Furthermore, the differences between the two groups in all outcome measures at the preintervention assessment were not significant.

The results for the primary outcome measures are shown in Table II. In the VR group, significant within-group effects were noted for the MoCA (P<0.001, effect size=1.03), EXIT-25 (P=0.01, effect size=0.65), CVVLT immediate and delayed recall (P<0.001, effect size=0.64 and P=0.002, effect size=0.89 respectively), and

TABLE I.—*Baseline demographic characteristics of the participants (N.=34).*

Characteristics	VR group	CPC group	P value
N. patients	18	16	
Age, years	75.5±5.2	73.1±6.8	0.257
Sex ratio, F/M	11/7	12/4	0.853
Height, cm	159.0±9.7	155.4±7.1	0.215
Body weight, kg	61.3±8.5	56.0±9.5	0.101
BMI, kg/m^2	24.4±4.2	23.2±3.6	0.384
Education	9.3±3.8	9.9±2.1	0.607
MMSE score	27.2±1.9	27.2±1.6	0.965
MoCA score	23.00±2.67	23.68±2.65	0.717
EXIT-25 score	6.61±2.76	6.25±2.04	0.588
CVVLT			0.504
Immediate recall	18.33±4.33	19.18±4.51	0.239
Delayed recall	4.27±2.16	4.68±2.15	0.790
IADL	18.16±2.33	17.81±2.40	0.838
Brain activation			
CH4	0.655±0.821	0.598±0.921	0.924
CH7	0.734±0.565	0.540±0.345	0.316
CH10	0.724±0.605	0.709±0.400	0.852
CH13	0.631±0.407	0.645±0.441	0.977
Left PFC	0.695±0.527	0.569±0.603	0.626
Left PFC	0.678±0.480	0.677±0.382	0.925
Bilateral PFC	0.686±0.476	0.623±0.442	0.729

The data are presented as the means±SD or numbers.
MMSE: Mini-Mental State Examination; MOCA: Montreal Cognitive Assessment; EXIT-25: The Executive Interview 25; CVVLT: Chinese Version of the California Verbal Learning Test; IADL: instrumental activities of daily living; CH: channel; PFC: prefrontal cortex.

IADL (P<0.001, effect size=0.87). The CPC group also showed improved scores on the EXIT-25 (P=0.001, effect size=0.76) and CVVLT immediate recall (P=0.011, effect size=0.72). Furthermore, a significant group × time effect was found for the IADL (P=0.006, effect size=0.217).

The results of the brain activation assessment by NIRS are shown in Table III. In the VR group, significant reductions were noted in CH7 (P=0.032, effect size=0.7), CH 13 (P=0.021, effect size=0.72), left prefrontal activation (P=0.029, effect size=0.72), right prefrontal activation (P=0.03, effect size=1.13) and bilateral prefrontal activation (P=0.015, effect size=0.83) after training. In the CPC group, significant reductions were noted in CH10 (P=0.002, effect size=1.06) and right prefrontal activation (P=0.025, effect size=0.69). There were no significant group × time effects between these two groups in terms of right, left, or bilateral prefrontal activation.

Discussion

The current study aimed at investigating the effects of VR-based physical and cognitive training on cognitive functions, IADL, brain activation, as well as comparing the VR intervention with a combined physical and cognitive

TABLE II.—*Comparisons of neurocognitive task performance in the VR group and the CPC group.*

Parameters	VR group (N.=18)			CPC group (N.=16)			Inter-group difference (time × group interaction)
	Pre	Post	P value	Pre	Post	P value	
MoCA score	23.00±2.67	25.20±2.37	<0.001*	23.68±2.65	24.87±2.91	0.078	0.181
EXIT-25 score	6.61±2.76	5.11±1.56	0.013*	6.25±2.04	5.00±2.12	0.010*	0.724
CVVLT							
Immediate recall	18.33±4.33	23.27±3.84	<0.001*	19.18±4.51	22.31±5.37	0.011*	0.149
Delayed recall	4.27±2.16	5.72±2.29	0.002*	4.68±2.15	5.25±2.54	0.155	0.115
IADL	18.16±2.33	19.77±2.12	<0.001*	17.81±2.40	18.25±2.04	0.219	0.006*

Data are presented as the means±SD.
MoCA: Montreal Cognitive Assessment; EXIT-25: Executive Interview 25; CVVLT: Chinese Version of the California Verbal Learning Test; IADL: instrumental activities of daily living.

TABLE III.—*Comparisons of the hemodynamic change (HbO) during the cognitive tasks in the two study groups.*

Brain activation	Virtual reality training group (N.=18)			Combined physical and cognitive training group (N.=16)			Between-group difference (time × group interaction)
	Pre	Post	P value	Pre	Post	P value	
CH4	0.655±0.821	0.395±0.300	0.283	0.598±0.921	0.488±0.406	0.656	0.739
CH7	0.734±0.565	0.371±0.351	0.032*	0.540±0.345	0.469±0.348	0.547	0.171
CH10	0.724±0.605	0.493±0.602	0.253	0.709±0.400	0.320±0.239	0.002*	0.523
CH13	0.631±0.407	0.358±0.328	0.021*	0.645±0.441	0.575±0.441	0.524	0.214
Left PFC	0.695±0.527	0.383±0.302	0.029*	0.569±0.603	0.479±0.358	0.593	0.378
Right PFC	0.678±0.480	0.425±0.381	0.030*	0.677±0.382	0.448±0.319	0.025*	0.850
Bilateral PFC	0.686±0.476	0.404±0.313	0.015*	0.623±0.442	0.463±0.277	0.133	0.455

Values are presented as mean±SE (mM×mm).
Right prefrontal cortex (PFC): average of CH4 and CH7; left PFC: average of CH10 and CH13; bilateral PFC: average of CH4, CH7, CH10 and CH13.

training program. To the best of our knowledge, this is the first training program using IADL-based VR as a means of intervention for MCI. First, we found that both groups improved their executive function and verbal memory (immediate recall). Second, significant improvements in MOCA and IADL were observed only after VR-based cognitive and physical training, while the dual physical and cognitive training group showed non-significant improvements in MOCA and IADL. Finally, the improved global cognitive function in the VR group was coupled with simultaneous decreases in the brain activation of the prefrontal areas.

The physiological effects of physical exercise on brain functioning include the release of the neurotrophic factor BDNF, increased blood flow, and beneficial metabolic effects. These outcomes might facilitate neuroplastic potentials and enhance learning during cognitive training.[34] Our results of CPC training were somewhat consistent with the literature,[11, 35] especially in terms of its positive effects on executive functions and memory. Executive functions refer to the higher-order cognitive abilities involved in planning, initiating, monitoring, and inhibiting goal-oriented behaviors[36] and are particularly critical to successfully executing IADL.[37] Memory (immediate, short and long delay memory) deficits often lead to difficulty completing IADL and accounted for much of the variance in functional impairment.[38] However, as suggested by the recent literature,[12] the significant improvement in executive functions and immediate memory after CPC training did not transfer to IADL. In fact, IADL require complex cognitive processing other than executive functions and immediate memory. Cognitive domains (such as visuospatial orientation and attention), physical capacity (such as visual acuity) and neuropsychiatric factors (such as depression or apathy) are also critical to IADL.[38, 39] It is also possible that the three-month CPC programs may be too short in duration to observe significant improvements in other cognitive functions and, thus, improvements in IADL.

A previous study revealed that functional task training could improve cognitive functions in older adults with MCI.[40] The advantage of the VR intervention might be that our IADL-based functional tasks effectively facilitated complex cognitive processing as participants repetitively practiced these functional tasks during the 12-week intervention. For example, "kitchen chef" was specifically designed to train for memory, visuospatial orientation and executive functioning, while participants prepared food as ordered with available kitchenware and ingredients. "Convenience store clerk" trained for memory, orientation and executive function as the participants retrieved and calculated the prices of the checkout items. Our program involved changes in cognitive load in the form of dual-task stimulation. Participants received immediate feedback and optimized their dual-task performances. We believe that dual-task stimulation with internalized feedback by VR may have effects on various cognitive functions. The other explanations are that VR provides a real-life scenario and coaching interactions tailored to individual performances. Therefore, the enjoyment and attractiveness of VR characteristics may increase their motivation and lead to extensive training effects resulting in cognitive improvement. Overall, these were the critical features that the combined physical and cognitive training program could not offer.

A prior systematic review found that only two out of nine ICT training studies reported improvements in IADL, and the effect size was relatively small for individuals with MCI.[41] However, our results showed significant within- and between-group differences in IADL after VR training. Compared to other ICT studies, our VR equipment provided the most immersive experience. In addition, our VR program followed the principle of Robert *et al.*'s recommendations[42] to emulate the activities of daily living. It is possible that the immersive experience in the IADL of our program facilitated the transfer of acquired functional capabilities into real-life IADL. As mentioned earlier, IADL required both cognitive and physical capacity. Apart from the IADL-based cognitive program we adopted, our physical training programs also contained many functional activities, such as stepping over obstacles, window cleaning, lighting fireworks, and goldfish grasping. Participants are required to be attentive to verbal instructions, and meanwhile, shift their weight, squat constantly, and reach toward a target at a given location as accurately and quickly as possible. These goal-directed actions not only improve physical capacities (e.g., muscle strength, balance and endurance) but also facilitate higher-ordered cognitive functions such as attention, visuospatial orientation and executive function to integrate information. Our improved cognitive functions in the VR group can illustrate the generalized training effect to IADL. Although the present VR program did not exactly mirror all the daily functional activities, the generalized effects on everyday problem-solving abilities found in the present study still support the idea that training effects can be transferred to untrained daily living activities.

Age-related neural declines may lead to a reduced quality of neural processing.[43] Different models have been proposed to explain the brain plasticity of the aging brain. The compensatory model suggests that the aging brain maintains optimal cognitive functions by relying on both increased activation of specialized areas and recruitment of additional brain networks.[44] Similar effects could be observed in elderly people with MCI. For example, Belleville *et al.* found that MCI increased activations in a large network (frontal, temporal and parietal areas), including areas activated prior to training and new alternative areas activated following training, while healthy controls showed mostly decreased activation as the consequence of training.[19] Thus, broader activation has been suggested as a compensatory strategy for a demented brain to maintain intact cognitive functions measured by behavioral data. The present study only measured the frontal areas of the brain, and thus we could not determine if there was any compensatory activation in other undetected areas. However, decreased activation in the brain after training could be seen as training-induced increase in neural efficiency, as a lower amount of energy or fewer brain networks were needed to achieve similar levels of cognitive performance due to the intervention. The concept of neural efficiency has been used in previous studies, revealing decreased activation of frontal-parietal areas and increased cognitive performance in older adults after training.[20, 45, 46] The present study extended the prior literature by showing that the brains of older adults with MCI, similar to healthy older adults, remain highly plastic.

Previous findings showed that 12 weeks of treadmill exercise decreases brain activation intensity during a semantic memory task and suggested that exercise may improve neural efficiency and cognitive function in MCI.[47] The cognitive improvement may be associated with the significantly decreased prefrontal hemodynamic response. In our CPC group, a marginal but nonsignificant decrease in the activation of the bilateral PFC was noted. We may suggest that the training effect of the CPC group may not be as sufficient as the VR group, and thus differences in pre- and posttrial hemodynamic response as well as global cognition were nonsignificant. In contrast, the VR group may benefit from the augmenting effect of our specific IADL-based training program in the VR context. Therefore, the improved neural efficiency of the bilateral PFC was noted after VR training.

Limitations of the study

There are some limitations in the present study. First, without follow-up assessment, it remains unknown whether the available intervention effect has been sustained over long periods. Second, the hemodynamic response was assessed only in the prefrontal areas, and there may be some intervention-induced changes in other brain areas that we were unable to detect. Third, the drop-out rate (19%) in the present study was greater than that as recommended by the PEDro score (15%). Of the 8 drop-out subjects, 3 dropped out due to health problems unrelated to training (*i.e.*, they needed to receive surgery or treatment in the hospital), and 5 dropped out due to low motivation (one complained our program did not inspire their interests, and 4 told us they could not continue the exercises because they were busy and had other commitments scheduled). Some important variables, such as depression and comorbidities, which might contribute to the drop-out rate, should be measured when screening for eligibility. For example, the Geriatric Depression Scale (GDS), a self-report assessment used to identify depression in the elderly, should be used to exclude depressive elderly, but we did not use this scale in the present study. Fourth, the Lawton IADL scale is a self-report measurement, though we checked with the caregivers of most participants. More sensitive tools to assess IADL performances may be required in further studies. Fifth, training intensity, such as the cognitive training program, is difficult to match. However, we monitored heart rate and perceived exertion and ensured that the session time of these two groups was equal. Finally, our VR program combined physical exercise and cognitive training sequentially, and the CPC program combined the physical exercise and cognitive training simultaneously. Although most articles have stated that simultaneous and sequential dual-task training programs were both effective in improving cognition and led to similar effects,[12, 48] the diverse treatment benefits could be attributed to different combinations of these methods and require further investigation.

Conclusions

The present study showed that cognitive functions of older adults with MCI benefited from 12 weeks of the VR intervention. A decreased activation in the prefrontal areas, indicative of increased neural efficiency, was also found in the VR training subjects. Furthermore, VR-based physical and cognitive training was superior in improving IADL compared to CPC training. The results support the use of VR-based physical and cognitive training in older adults with MCI.

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