A randomized controlled trial of combined executive function and memory training on the cognitive and noncognitive function of individuals with mild cognitive impairment: Study rationale and protocol design

Haifeng Zhang\textsuperscript{a,b,c,d}, Jing Wang\textsuperscript{a,b,c,d,*}, Tingting Sun\textsuperscript{a,b,c,d}, Zhijiang Wang\textsuperscript{a,b,c,d}, Xiaozhen Lyu\textsuperscript{a,b,c,d}, Xin Yu\textsuperscript{a,b,c,d}, Huali Wang\textsuperscript{a,b,c,d,**}

\textsuperscript{a}Clinical Research Division, Peking University Institute of Mental Health (Sixth Hospital), Beijing, China
\textsuperscript{b}National Clinical Research Center for Mental Disorders, Peking University, Beijing, China
\textsuperscript{c}Key Laboratory of Mental Health, Ministry of Health, Peking University, Beijing, China
\textsuperscript{d}Beijing Dementia Key Laboratory, Beijing, China

Abstract

Introduction: Cognitive training has attracted considerable attention as a safe, economical, and scalable nonpharmacologic intervention in patients with mild cognitive impairment (MCI). However, no study has yet placed sufficient emphasis on the training of executive function. The present study aimed to evaluate whether memory training combined with executive training could lead to improved cognitive and noncognitive performance in patients with MCI. Furthermore, we will explore the neural correlates underlying the changed performances.

Methods: The proposed study is a randomized controlled trial that will include 120 patients with MCI. The eligible patients will be randomized to either an intervention group or a waitlist control group. The intervention group will receive computerized combined training (executive function and memory) for 96 sessions for more than 24 weeks. The control group will receive no intervention during the research period. Behavior data collection and a magnetic resonance imaging/electroencephalogram/near-infrared spectroscopy scan will be performed at baseline and after 24 weeks of intervention.

Results: The study is currently ongoing. Recruitment began in July 2017 and will conclude in December 2018.

Discussion: If combined training results in positive changes to cognitive function and noncognitive function in patients with MCI, this might represent a new approach to delay the cognitive decline or even provide a potential method for dementia prevention. Furthermore, the evaluation of any training-related structural changes or functional changes will help to reveal the mechanisms underlying the combined cognitive training.

Trial registration: This study was registered with Clinicaltrials.gov (Identifier: NCT03232047, August 18, 2017).

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Keywords: Mild cognitive impairment; Dementia; Computerized; Cognitive training; Memory; Attention; Executive function

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*Corresponding author. Tel.: +86-10-82801983; fax: +86-10-62011769.
**Corresponding author. Tel.: +86-10-82802837; fax: +86-10-62011769.
E-mail address: wangjing1796@bjmu.edu.cn (J.W.), huali_wang@bjmu.edu.cn (H.W.)
1. Introduction

Mild cognitive impairment (MCI) is a borderland between the cognitive changes of aging and very early dementia [1]. Cumulative dementia incidence is 14.9% in individuals with MCI older than 65 years after merely 2 years of follow-up [2]. Although some patients could revert to normal cognition after the diagnosis of MCI, they still have a 6.6 times higher risk of developing dementia than the normal cognition population after a 5-year follow-up [3]. Thus, MCI represents a critical window of opportunity for the prevention of dementia.

Cognitive training refers to a series of repeated and standardized tasks targeting specific cognitive domains to solve inherent problems of patients [4]. It is based on the theory of neuroplasticity, which means that the brain still can modify its structure and function in response to external or internal stimulations [5]. Therefore, it is considered to be a potentially effective approach to prevent further cognitive decline in patients with MCI [6].

A number of cognitive training studies have focused on memory deficits, which is one of the major manifestations of patients with MCI, and found that memory training could improve memory performance [7–9]. For example, Belleville et al. [7] reported that 8 weeks of episodic memory training sessions significantly enhanced the subjective memory and well-being of patients with MCI. Hampstead et al. [8] also reported that 2 weeks of explicit memory training led to improved memory for face-name pairs in patients with MCI. Furthermore, the memory training might induce the transfer effect, as Savulich et al. [9] found that 4 weeks of cognitive training using a novel memory game on an iPad not only robustly improved episodic memory but also improved general cognition and visual-spatial abilities of patients with MCI. A meta-analysis study showed that memory strategy training for older adults induced a moderate training effect (0.43 standard deviation [SD]; 95% confidence interval, 0.29–0.57) on overall episodic memory function compared with that in control groups [10].

Although memory deficits are a core symptom of MCI, the cognitive deficits are not limited to memory function. The other aspects of cognitive function, such as attention and executive function, are also impaired in patients with MCI [11–13]. The deficits of other cognitive domains will affect memory performance. Encoding, storage, and retrieval of information require attention, and the use of mnemonic strategies requires executive function [14]. In addition, the deficits of executive function will also affect daily living of patients with MCI [15]. But, as two recent meta-analyses reported, there is still no study on the sufficient training of executive function in patients with MCI [6,16].

Previous studies suggest that combined training could result in a broader training effect in healthy older adults and patients with MCI [16–18]. In addition, an enhanced functional connectivity between three higher cognitive functional networks, that is, the default mode network, the salience network, and the central executive network, was observed after the combined training [19]. Therefore, we hypothesize that the combined executive function and memory training could help improve the cognitive ability and noncognitive function in patients with MCI.

The primary objective of the study is to investigate the extent to which a combined intervention could affect cognition in patients with MCI. The secondary objective is to explore whether our intervention could affect the noncognitive function (the mood and the activities of daily living [ADL]) of the participants. The tertiary objective is to investigate the neural substrate underlying the intervention, which is measured by magnetic resonance imaging (MRI)/electroencephalogram (EEG)/near-infrared spectroscopy (NIRS) scan.

2. Methods

2.1. Study design

We have begun to conduct a randomized controlled trial (ClinicalTrials.gov identifier: NCT03232047) by enrolling 120 patients with MCI from the Dementia Care and Research Center of the Peking University Institute of Mental Health (PKU-IMH) and community health centers.

The study consists of two arms: a computerized combined cognitive training intervention group with guidance from a coach, and a waitlist control group who will receive no training during the research period. The waitlist group will, however, receive the training after the follow-up assessment as a compensation.

2.2. Participants

Participants are nondemented, nondepressed individuals aged 60 to 89 years who meet the International Working Group MCI criteria [20], having subjective memory complaints and a Mini-Mental State Examination (MMSE) score of no less than 24, a Montreal Cognitive Assessment (MoCA) score of less than 26, a Clinical Dementia Rating scale of 0.5, and independent in daily function. The exclusion criteria are a current or past neurologic disorder or a current neuropsychiatric disorder affecting cognition, take cognitive enhancers, and any physical condition that could preclude regular attendance and full participation in the intervention program. Complete inclusion and exclusion criteria are listed in Table 1.

The work is being carried out according to the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The ethics committee of PKU-IMH approved this study (number 2017-1-25-3). All subjects will be fully informed of the study protocol and have to sign the written informed consent.

2.3. Randomization and blinding

A biostatistician, independent of our research, from the Research Center for Clinical Epidemiology (Peking
The combined cognitive training included memory (i.e., I, Recall the digits; II, Recall the sequence of the balls; and III, Match the colored balls.) and executive function (IV, Tower of Hanoi; V, Sudoku; VI, Click on the colored balls.) (Table 2). There are eight tasks in total.

The memory training tasks (I, II, and III) are rehearsal-based approaches designed to load on memory cognitive, with repetition of the process of encoding, storage, and retrieval without explicit teaching of memory [21]. The development of the executive function training is based on a model that highlights three separate but related executive functions (“shifting,” “updating,” and “inhibition”) [22]. Task VI focuses on shifting, and task VII and VIII focus on inhibition. Task IV and V further focus on planning and problem solving, which are closely related to daily activities of living.

The tasks run on an android system tablet-computer, which has a 10.1-inch touchscreen. The intervention is held in group sessions led by a coach who will teach the participants on how to use the tablet and what are the tasks involved, but not on how to finish the tasks.

As we had mentioned, previous cognitive training studies in patients with MCI did not put sufficient training on the executive function. The mean training duration and dose are 10.49 weeks (SD = 7.47) and 27.57 hours (SD = 24.60), respectively [16]. Therefore, we increased the duration and dose of the intervention to see whether sufficient training could enhance executive function. The training period is chosen to be 24 weeks and dose to be 96 hours. In detail, the intervention consists of 96 sessions of 60 minutes each given four times per week over a period of 24 weeks. Each session consists of two domains, each lasting 30 minutes. Each participant will have the identical training schedule from the first to the last session. To further improve the retention, the coach will tell the participants the next training date when the participants finished one training session. To improve the compliance, the participants were asked via phone to complete the subsequent session within 48 hours if they missed one or more sessions.

There are five levels of difficulty in each task, and there are 10 same-difficulty rounds in each level. If the participants correctly answered 80% or more rounds, the difficulty level will increase conversely, whereas if the participants correctly answered fewer than 50% of the rounds correctly, the difficulty level will decrease. If the participants correctly answered 50% to 80% of the rounds, the difficulty level of the next trial will be the same to maintain the challenge and maximize performance.

The tablet-computer provides access to the Internet during the training so that the training record can be uploaded to the server. In addition, a paper record will also be kept for a double check.

2.5. Outcome measurement

The primary outcome measure is the composite z score for working memory, which consists of digit span and spatial span. Working memory is typically defined as the ability to maintain and manipulate information over short periods of time [23]. One widely accepted model of working memory is Baddeley’s four major components: (1) two short-term storage buffer for visual and verbal
information; (2) a central executive component that guides
the manipulation and transformation of information held
within the storage buffers; and (3) the episodic buffer
[24]. The core of working memory is the central executive
component, which plays a major role in the performance of
working memory. Thus, we believe that our training, which
applies sufficient executive function training along with the
memory training, will strongly affect the core (the central
components) of working memory function, and eventually
result in the improvement of working memory performance
in patients with MCI.

Composite outcome measures, which can improve the
power and trial efficacy, have been proposed as outcome
measures for clinical trials [25,26]. Furthermore, the US
Food and Drug Administration has encouraged the use of
composite cognitive tests as outcome measures in
preclinical stage Alzheimer’s disease trials [27].

The secondary outcome measures are as follows: (1) the
composite z score for overall cognition, which included all
the cognitive tests; (2) the composite z score for the general
cognitive function, which includes the MoCA and MMSE;
(3) the self-evaluated memory ability, which uses overall
contentment or satisfaction with one’s own memory ability
(Multifactorial Memory Questionnaire Contentment); (4)
the ADL, which uses the ADL scale; (5) the mood status,
which uses the Patient Health Questionnaire-9; (6) the social

| Tasks                        | Targeted domain      | Trained sessions* | Difficulty levels/rounds | A brief description of the tasks                                                      |
|------------------------------|----------------------|-------------------|--------------------------|---------------------------------------------------------------------------------------|
| Recall the sequence of the balls | Memory              | 3                 | 5/10                     | To start, balls with digits on their surface are shown on the screen. Then, the digits disappear whereas the balls are still at the same position. The participants are asked to click the balls in ascending or descending turn according to their memory. With more balls shown, the difficulty level increases |
| Recall the digits            | Memory              | 4                 | 5/10                     | To start, a group of digits is shown, and then another group is shown on the screen. A third group that consists of parts of groups one and two is shown. The participants are asked to select the numbers that were shown both in the first and second group from the third group according to their memory. With more digits shown in the groups, the difficulty level increases |
| Match the colored balls      | Memory              | 1                 | 5/10                     | To start, balls with digits on their surface are shown. The digits will disappear seconds later. The participants are asked to select the balls showing the same digits according to their memory. With more balls shown, the difficulty level increases |
| Find the persons who look different | Executive function | 3                 | 5/10                     | To start, cartoon faces are shown on the screen. The photographs are different from others (nose, mouths, hair, glasses, and so forth). The participants are asked to click the ones that are different. With more photographs shown, the difficulty level increases |
| Hunt for the objects         | Executive function  | 1                 | 5/10                     | To start, hundreds of objects that belong to different categories are shown, and every category includes 10 objects. The participants are asked to select some number of objects of the same category. With more objects they are asked to find, the difficulty level increases |
| Click on the colored balls alternately | Executive function | 2                 | 5/10                     | To start, balls with digits and colors (red or green) are shown on the screen. The participants are asked to click the balls in color switching and number ascending or descending turn until finished. With the more number of balls, the difficulty level increases |
| Tower of Hanoi              | Executive function  | 2                 | 5/1 | This task consists of three rods and some disks of different sizes, which can slide onto any rod. The objective of the puzzle is to move the entire stack to another rod. With more disks to be placed on rods, the difficulty level increases |
| Sudoku                      | Executive function  | 4                 | 5/10                     | The goal of Sudoku is to fill a 9 × 9 grid with digits, so that each row, column, and 3 × 3 section contains all the digits between 1 and 9. With more grids, the difficulty level increases |

*Every four sessions are a loop and cover all the eight tasks. The number indicates the sequence in the four sessions.
cognition score change, which uses the Eye Basic Emotion Discrimination Task and the Eye Complex Emotion Discrimination Task; (7) the brain activity change, which uses an EEG; (8) the cerebral blood flow change, which uses NIRS; (9) the brain-derived neurotrophic factor change, which uses the serum; and (10) the structural and the functional imaging change, which uses MRI (Tables 3 and 4).

2.6. MRI, EEG, and NIRS acquisition

At baseline and trial completion, the MRI/EEG/NIRS data will be obtained following the behavioral assessment. MRI acquisition will be conducted using a 3.0 T GE MR750 scanner (Boston, MA) with an eight-channel sensitivity encoding head coil (SENSE factor = 2.4) at the modified expanded electrodes mounted in an elastic cap (Brain Product, Munich, Germany) according to the modified expanded 10 to 20 system each electrode will be referenced online to the vertex (Cz). The relative concentration changes in oxy-Hb and deoxy-Hb will be measured using a 52-channel NIRS optical topography system (ETG-4000, Hitachi Medical Co, Tokyo, Japan). The system uses two wavelengths of near-infrared light (695 and 830 nm) and calculates the amount of absorbed near-infrared light based on the modified Beer-Lambert law. The EEG and NIRS data will be collected at the PKU-IMH.

| Measure                  | Assessment tool          | 0 mo | 6 mo |
|-------------------------|--------------------------|------|------|
| General information     | Demographic information  | ×    |      |
| Executive function      | Spatial span             | ×    |      |
|                         | Digit span               | ×    | ×    |
|                         | Number sequencing        | ×    | ×    |
|                         | PASAT                    | ×    |      |
|                         | Stroop test              | ×    |      |
|                         | NCT                      | ×    |      |
|                         | TMT                      | ×    |      |
|                         | DSC                      | ×    | ×    |
|                         | Color Trails test        | ×    | ×    |
|                         | Go/no go                 | ×    |      |
|                         | Contrast program         | ×    |      |
|                         | Verbal fluency           | ×    |      |
| General cognition       | MMSE, MoCA              | ×    |      |
| function                |                          |     |      |
| Episodic memory         | MBT                      | ×    |      |
| Memory self-evaluation  | MMQ-contentment          | ×    | ×    |
| Social cognition        | EBEDE, ECEDE            | ×    |      |
| ADL                     | The Lawton IADL          | ×    |      |
| Mood                    | PHQ-9                    | ×    |      |
| MRI/EEG/NIRS            | Structure and functional tools* | × | × |
| Blood sampling          | BDNF                     | ×    |      |

Abbreviations: BDNF, brain-derived neurotrophic factor; DSC, digit symbol coding; EEG, electroencephalogram; EBEDE, Eye Basic Emotion Discrimination Task; ECEDE, Eye Complex Emotion Discrimination Task; HVLT-R, Hopkins Verbal Learning Test–Revised; IADL, Instrumental Activities of Daily Living Scale; MBT, Memory Binding Test; MMQ, Multifactorial Memory Questionnaire; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; NCT, Number Cancellation Test; NIRS, near-infrared spectroscopy; PASAT, Paced Auditory Serial Addition Test; PHQ-9, Patient Health Questionnaire-9; TMT, Trail Making Test.

NOTE. × Indicates the point of the trial when the assessments will take place.

*Detailed in Table 4.
no training. Finally, the postintervention measurement will be assessed 24 weeks after randomization (Fig. 1).

2.8. Statistical analysis

2.8.1. Sample size
The primary outcome of interest in this study is the change in working memory after 24 weeks. The calculation of sample size is based on a superiority test, as the aim of this study is to show that computerized cognitive training is superior to the waitlist. The effect size used to calculate the sample size is 0.7, based on the studies which show that the effect size of working memory training for MCI is 0.74 [0.32, 1.15] and executive function is 0.575 [0.093, 1.056] [6,16]. We expect that the SD of the intervention group and the control group would be 1.3 and 0.5, respectively (with a two-tailed t test, $\alpha = 0.05$, $1 - \beta = 0.80$). We will need a sample size of 50 participants for each group. If the maximum dropout rate allowed is 20%, we will need 60 participants for each group. Thus, the total sample size for this study will be 120 participants.

2.8.2. Preprocessing of MRI/EEG/NIRS data
Before subjecting raw data to statistical analysis, we will perform preprocessing steps for the MRI/EEG/NIRS data.

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**Fig. 1. Overview of study procedure. Abbreviations: DCRC, Dementia Care and Research Center; PKU-IMH, Peking University Institute of Mental Health.**
2.8.3. Statistical considerations

The analysis will be conducted based on the consolidated standards of reporting trial statement regarding eHealth [28]. The analysis will be performed according to the intention-to-treat principle and per protocol set. The per protocol set was defined as those participants who completed more than 70% of sessions of the intervention originally allocated and completed all the required assessments. We will compare characteristics of the dropout participants to the completed participants. We will further perform sensitivity analyses of completers and per-protocol analyses to examine the potential for dropout participants and imputation to bias the results.

The distribution of all covariates of interest to identify outliers and assess skewness will be assessed. Then, the composite $z$ scores for working memory, composite $z$ scores for overall cognition, and composite $z$ scores for general cognition will be created.

Regarding the efficacy, we will analyze the change in primary outcome and secondary outcomes in the intervention group ($\Delta_{\text{intervention}}$) and control group ($\Delta_{\text{control}}$) by using independent Student’s $t$ tests or the Mann-Whitney $U$ test for continuous outcomes.

Behavior variables, EEG data, and NIRS data will be assessed in Statistical Package for Social Sciences (SPSS) software (version 20.0 for Windows, SPSS Inc, Chicago, IL), and the significance level was set at $P < .05$. MRI/EEG/NIRS data will be assessed in independent Student’s $t$ tests in statistical parametric mapping. The statistical significance level was set at $P < .001$.

To find the neural correlates underlying the intervention, the correlations will be calculated between the change in the MRI/EEG/NIRS data and the change in the behavior data.

2.8.4. Safety analysis

None of the published trials on cognitive training reviewed by the committee found adverse effects, and there is little evidence to indicate that participating in these activities has negative consequences [29]. However, safety issues of this intervention will be carefully considered. We will record all the adverse events and negative consequences. The safety analysis will include descriptive statistics for all randomized participants.

3. Discussion

In this study, we will investigate whether combined cognitive training (combined memory and executive function) could prevent or delay cognitive impairment in an older population at high risk of dementia. We will further explore the potential mechanism underlying this intervention.

One major challenge in cognitive training is the insufficient training of executive function, which we thought might hamper the efficacy of the training [6,8,9,30,31]. Our study will combine executive function training (2/3 training time) with memory training (1/3 training time) to find whether the combined executive function training could maximize the training effect among patients with MCI.

There are some hypotheses about the neural correlates underlying combined training. For example, one hypothesis suggests that combined training may recruit alternate networks as functional support to help primary functional network process load demands [32,33]. However, this hypothesis is far from conclusive. We will include MRI/EEG/NIRS scan along with cognitive and mood assessment, with an aim to provide more evidence for the underlying neural correlate.

Although the advantages of cognitive training are obvious, one major challenge for generalization is the lack of training services. Traditional training requires face-to-face teaching by specially trained coaches, and only a few large cities in China can provide this service. Thus, it is extremely difficult for the people in rural areas to use this service. The delivery of cognitive training programs may, therefore, require a more convenient method. Previous studies have shown that tablet-based cognitive training can provide the participants with high levels of enjoyment and desire to continue training. Our training program, which is also delivered by tablet-computer and use adaptive tasks, might thus be easy for future patients with MCI to access.

Several limitations to this study should be noted. First, we use intermediate outcomes instead of incidence of dementia because our study time is relatively short compared with the long duration of the disease. Thus, we could not directly answer the question of whether the combined training could delay the onset of dementia. Second, considering the feasibility, we did not design an active control group. The increased contact time and interaction with the training coach and other elderly might positively impact cognition or offer some additional confounding social benefit. However, to minimize the social interaction, we are using computer-assisted cognitive training, which means that the participants are only interacting with the computer tasks but not with the coach. The coach will only help the participants to solve the technique problems and will not participate in the training process. Third, because of our design of waitlist as the control group, we will provide compensate training for the control group after the training period. It will not be possible for us to compare the longer follow-up effect of training and without training difference, which is shown in the Advanced Training in Vital Elderly study [34]. However, the primary objective of the study is to investigate the extent to which a combined intervention could affect cognition in patients with MCI. We will explore the longer effect of cognitive training on cognition or risk of dementia in our future research. Finally, although this study is being randomized and well controlled, the participants are not blinded. Therefore, they may disclose their allocation sequence to the evaluators; thus, the observer bias may be present in the behavioral outcome measures.

In summary, our study, which combines executive function and memory training and is delivered on an
easy-access tablet-computer, will be able to provide new and unique knowledge. A new approach to delay the deterioration of memory decline may be feasible.

3.1. Trial status

The study is currently ongoing. Recruitment began in July 2017 and will conclude in December 2018.

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RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed previously published literature in the field of cognitive training and patients with mild cognitive impairment. Interventional research evaluating the effect of cognitive training, especially on executive function, has provided inconclusive results.

2. Interpretation: There is a need for future studies to pay more attention to executive function to ensure participants are gaining sufficient executive function training. Furthermore, comprehensive outcome measures related to the intervention need to be measured, including cognitive tests, noncognitive tests, magnetic resonance imaging biomarkers, electroencephalogram biomarkers, near-infrared spectroscopy biomarkers, and blood-based biomarkers.

3. Future directions: This article describes the protocol of a trial evaluating the effect of combined executive function and memory training on cognitive function and noncognitive function and the potential mechanism underlying the intervention. Results from this study will be vital in the design and implementation of the future nonpharmacologic intervention.

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