Alzheimer's & Dementia: Translational Research & Clinical Interventions 4 (2018) 556-564

Featured Article

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[a,b,c,d], Jing Wang[a,b,c,d,**], Tingting Sun[a,b,c,d], Zhijiang Wang[a,b,c,d], Xiaozhen Lyu[a,b,c,d], Xin Yu[a,b,c,d], Huali Wang[a,b,c,d,*]

[a]*Clinical Research Division, Peking University Institute of Mental Health (Sixth Hospital), Beijing, China*
[b]*National Clinical Research Center for Mental Disorders, Peking University, Beijing, China*
[c]*Key Laboratory of Mental Health, Ministry of Health, Peking University, Beijing, China*
[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).

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

Conflict of interest: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare no financial relationships with any organizations that might have an interest in the submitted work and no other relationships or activities that could appear to have influenced the submitted work.

*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.)

https://doi.org/10.1016/j.trci.2018.09.004

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

Table 1
Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Right handed	Participation in any other studies
89 ≥ Age ≥ 60	Axis I disorders listed in the DSM-IV
CDR ≤ 0.5	Visual impairment cannot be corrected using glasses
HAMD < 12	Hearing impairment cannot corrected by hearing aids
MMSE ≥ 24; MoCA ≤26	Any physical condition that could preclude regular attendance
Intact activities of daily living (ADL ≤ 26)	Take cognitive enhancers, antidepressants in the last month
Have at least primary school education (≥5 y)	Any neurologic disorders that could affect cognitive function
Meet the International Working Group MCI criteria	Diagnosis of dementia (according to ICD-10 and NINCDS-ADRDA)

Abbreviations: ADL, activities of daily living; CDR, Clinical Dementia Rating; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th edition; HAMD, Hamilton Rating Scale for Depression; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.

University Third Hospital) generated the random allocation sequence (with a block size of four) using R Software version 3.4.2. Sealed envelopes, which are opaque and sequentially numbered, are used to conceal the random allocation sequence. The opaque sealed envelopes, with participants' enrollment order printed outside and randomly assigned group printed inside, will be numbered consecutively and attached to a strain. Researchers will enroll the eligible participants after baseline assessment, then separate and open each envelope from the strain in the sequence corresponding to the participant's baseline assessment order, and assign the eligible participant into either the intervention group or the waitlist control group. To ensure that the randomized sequence allocation was strictly followed, when the researcher opens the envelope, he/she will write the name, date, and reason on the bottom of the envelope.

The behavioral data evaluators and MRI/EEG/NIRS scanners are blinded to the group assignments.

2.4. Interventions

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 alternately; VII, Hunt for the objects; and VIII, Find the persons who look different.) (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

Table 2
Study tasks

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.

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

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 Peking University Third Hospital Neuroimaging Center.

The EEG will be recorded from 64 scalp sites using tin 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.

Table 3
Outline of study assessments and timelines

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	×	×
	Contrasting program	×	×
	Verbal fluency	×	×
General cognition function	MMSE, MoCA	×	×
Episodic memory	MBT	×	×
Memory self-evaluation	MMQ-contentment	×	×
Social cognition	EBEDT, ECEDT	×	×
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; EBEDT, Eye Basic Emotion Discrimination Task; ECEDT, 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 Task; PHQ-9, Patient Health Questionnaire-9; TMT, Trial Making Test.

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

*Detailed in Table 4.

Table 4
Outline of neuroimaging assessments

Assessment tools	Outcome
Structural MRI	
	1. Voxel-based morphometry
	2. GM volume
	3. Cortical thickness
Resting state functional MRI	
	1. Amplitude of low frequency fluctuations
	2. Graph theoretical analysis of brain networks
	3. Bilateral hippocampal connectivity
	4. Posterior cingulate functional connectivity map
	5. Default mode network
	6. Frontal network
EEG	
	1. Clustering coefficient
	2. Average path length
NIRS	The blood volume change in frontal lobe

Abbreviations: EEG, electroencephalogram; GM, gray matter; MRI, magnetic resonance imaging; NIRS, near-infrared spectroscopy.

2.7. Procedure

Participants are being recruited from the nearby community health centers through paper poster delivery in the community and online forums about the research project through WeChat subscriptions. Participants interested in this project will go to the community health centers to complete a screening questionnaire, which includes demographic data, MMSE, MoCA, ADL, and the Hamilton Rating Scale for Depression. Laboratory assessments such as complete blood count, electrolyte panel, calcium, serum urea nitrogen, creatinine, glucose, vitamin B12, and thyrotropin will be evaluated. Then, the individuals will be invited to undergo a 45 to 60 minutes of neurologic and physical examination and a 30 minutes in-person diagnosis by the physicians of Dementia Care and Research Center of the PKU-IMH in the local community health center. If the person was diagnosed with MCI, they will be invited by the physician to participate in the project, and the patients with MCI who are willing to participate will be assessed for eligibility. The patients who met the eligibility requirements will be assessed with a baseline assessment, and then given the MRI/EEG/NIRS scan within 2 weeks. They will be allocated to either the intervention group or the control group according to the random number from the sealed envelope. Then, the intervention group will receive the intervention, and the control groups will have

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.

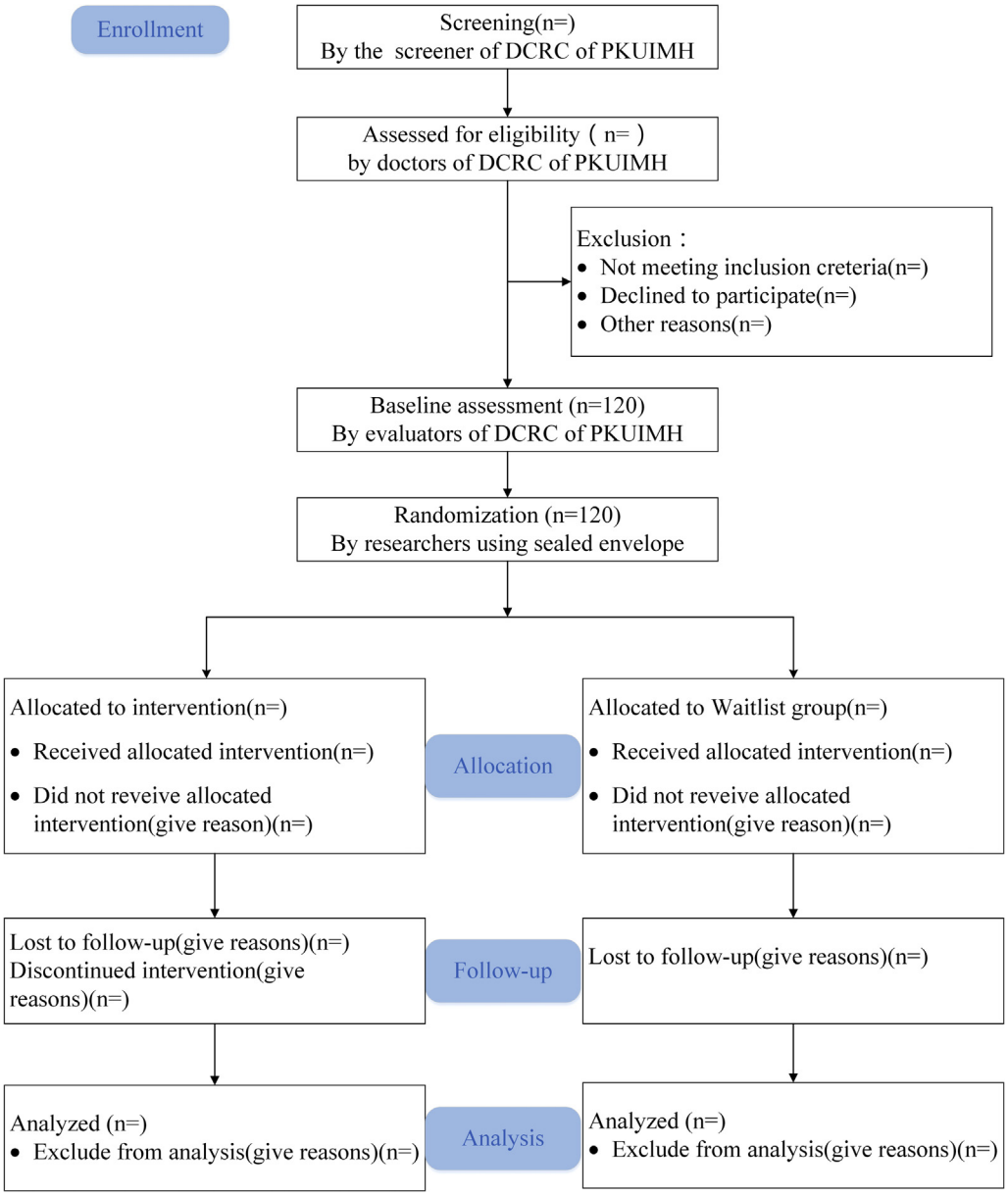

Fig. 1. Overview of study procedure. Abbreviations: DCRC, Dementia Care and Research Center; PKU-IMH, Peking University Institute of Mental Health.

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.

Acknowledgments

This work was supported by the Beijing Municipal Science and Technology Commission (grant number Z161100000516001) and the National Natural Science Foundation of China (grant numbers 81171018 and 81701777). The authors acknowledge Beijing Neowave Technology Co, Ltd, who codeveloped the training system. H.Z. thanks the China Scholarship Council (CSC) for the financial support (No 201706010329) to be a visiting PhD student at the University College London, UK.
Author contributions: All authors contributed to design and drafting of the report. H.W., J.W., and X.Y. formulated the research question. H.Z. and H.W. wrote the first draft of the article. H.W. was the Principal Investigator for this study and submitted the report for publication. The publication is approved by all authors.

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.

References

[1] Petersen RC. Mild cognitive impairment. Continuum (Minneap Minn) 2016;22:404–18.
[2] Petersen RC, Lopez O, Armstrong MJ, Getchius TSD, Ganguli M, Gloss D, et al. Practice guideline update summary: mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 2018;90:126–35.
[3] Roberts RO, Knopman DS, Mielke MM, Cha RH, Pankratz VS, Christianson TJ, et al. Higher risk of progression to dementia in mild cognitive impairment cases who revert to normal. Neurology 2014;82:317–25.
[4] Gates N, Valenzuela M. Cognitive exercise and its role in cognitive function in older adults. Curr Psychiatry Rep 2010;12:20–7.
[5] Belleville S, Clement F, Mellah S, Gilbert B, Fontaine F, Gauthier S. Training-related brain plasticity in subjects at risk of developing Alzheimer's disease. Brain 2011;134:1623–34.
[6] Hill NT, Mowszowski L, Naismith SL, Chadwick VL, Valenzuela M, Lampit A. Computerized cognitive training in older adults with mild cognitive impairment or dementia: A systematic review and meta-analysis. Am J Psychiatry 2016;174:329–40.
[7] Belleville S, Gilbert B, Fontaine F, Gagnon L, Menard E, Gauthier S. Improvement of episodic memory in persons with mild cognitive impairment and healthy older adults: Evidence from a cognitive intervention program. Dement Geriatr Cogn Disord 2006;22:486–99.
[8] Hampstead BM, Sathian K, Moore AB, Nalisnick C, Stringer AY. Explicit memory training leads to improved memory for face-name pairs in patients with mild cognitive impairment: Results of a pilot investigation. J Int Neuropsychol Soc 2008;14:883–9.
[9] Savulich G, Piercy T, Fox C, Suckling J, Rowe JB, O'Brien JT, et al. Cognitive training using a novel memory game on an iPad in patients with amnestic mild cognitive impairment (aMCI). Int J Neuropsychopharmacol 2017;20:624–33.
[10] Gross AL, Parisi JM, Spira AP, Kueider AM, Ko JY, Saczynski JS, et al. Memory training interventions for older adults: A meta-analysis. Aging Ment Health 2012;16:722–34.
[11] Traykov L, Raoux N, Latour F, Gallo L, Hanon O, Baudic S, et al. Executive functions deficit in mild cognitive impairment. Cogn Behav Neurol 2007;20:219–24.
[12] Okonkwo OC, Wadley VG, Ball K, Vance DE, Crowe M. Dissociations in visual attention deficits among persons with mild cognitive impairment. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn 2008;15:492–505.
[13] Petrova M, Raycheva M, Zhelev Y, Traykov L. Executive functions deficit in Parkinson's disease with amnestic mild cognitive impairment. Am J Alzheimers Dis Other Demen 2010;25:455–60.
[14] Buckner RL. Memory and executive function in aging and AD: Multiple factors that cause decline and reserve factors that compensate. Neuron 2004;44:195–208.
[15] Aretouli E, Brandt J. Everyday functioning in mild cognitive impairment and its relationship with executive cognition. Int J Geriatr Psychiatry 2010;25:224–33.
[16] Sherman DS, Mauser J, Nuno M, Sherzai D. The efficacy of cognitive intervention in mild cognitive impairment (MCI): A meta-analysis of outcomes on neuropsychological measures. Neuropsychol Rev 2017;27:440–84.
[17] Cheng Y, Wu W, Feng W, Wang J, Chen Y, Shen Y, et al. The effects of multi-domain versus single-domain cognitive training in non-demented older people: A randomized controlled trial. BMC Med 2012;10:30.
[18] Li B, Zhu X, Hou J, Chen T, Wang P, Li J. Combined cognitive training vs. memory strategy training in healthy older adults. Front Psychol 2016;7:834.
[19] Cao W, Cao X, Hou C, Li T, Cheng Y, Jiang L, et al. Effects of cognitive training on resting-state functional connectivity of default mode,

salience, and central executive networks. Front Aging Neurosci 2016; 8:70.
[20] Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, et al. Mild cognitive impairment—beyond controversies, towards a consensus: Report of the International Working Group on mild cognitive impairment. J Intern Med 2004; 256:240–6.
[21] Hampstead BM, Mosti CB, Swirsky-Sacchetti T. Cognitively-based methods of enhancing and maintaining functioning in those at risk of Alzheimer's disease. J Alzheimer's Dis 2014;42(Suppl 4):S483–93.
[22] Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: A latent variable analysis. Cogn Psychol 2000;41:49–100.
[23] Baddeley AD, Hitch G. Working memory. Psychol Learn Motiv 1974; 8:47–89.
[24] Baddeley A. Working memory: Theories, models, and controversies. Annu Rev Psychol 2012;63:1–29.
[25] Edland SD, Ard MC, Li W, Jiang L. Design of pilot studies to inform the construction of composite outcome measures. Alzheimers Dement (N Y) 2017;3:213–8.
[26] Donohue MC, Sperling RA, Salmon DP, Rentz DM, Raman R, Thomas RG, et al. The preclinical Alzheimer cognitive composite: Measuring amyloid-related decline. JAMA Neurol 2014;71:961–70.
[27] US Department of Health and Human Services. Early Alzheimer's disease: Developing drugs for treatment guidance for industry: Draft guidance; 2018.
[28] Eysenbach G, CONSORT-EHEALTH Group. CONSORT-EHEALTH: Improving and standardizing evaluation reports of Web-based and mobile health interventions. J Med Internet Res 2011;13:e126.
[29] National Academies of Sciences, Engineering, and Medicine. Preventing cognitive decline and dementia: A way forward. Washington (DC): National Academies Press; 2017.
[30] Belleville S. Cognitive training for persons with mild cognitive impairment. Int Psychogeriatr 2008;20:57–66.
[31] Lampit A, Hallock H, Valenzuela M. Computerized cognitive training in cognitively healthy older adults: A systematic review and meta-analysis of effect modifiers. PLoS Med 2014;11:e1001756.
[32] Ciarmiello A, Gaeta MC, Benso F, Del Sette M. FDG-PET in the evaluation of brain metabolic changes induced by cognitive stimulation in aMCI subjects. Curr Radiopharm 2015;8:69–75.
[33] Barban F, Mancini M, Cercignani M, Adriano F, Perri R, Annicchiarico R, et al. A pilot study on brain plasticity of functional connectivity modulated by cognitive training in mild Alzheimer's disease and mild cognitive impairment. Brain Sci 2017;7:50.
[34] Edwards JD, Xu H, Clark DO, Guey LT, Ross LA, Unverzagt FW. Speed of processing training results in lower risk of dementia. Alzheimers Dement 2017;3:603–11.