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Development and effectiveness of virtual interactive working memory training for older people with mild cognitive impairment: a single-blind randomised controlled trial

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Abstract

Background: memory training is a potential intervention for retaining memory and reducing dementia risk in older adults with mild cognitive impairment (MCI).
Objective: this study examined the effect of virtual interactive working memory training (VIMT) in older adults with MCI.
Design: single-blind, two-arm parallel-group, randomised controlled design.
Setting: retirement homes, institutions, and communities.
Subjects: a total of 66 older adults with MCI were recruited (mean age: 78.5 ± 7.6 years).
Methods: participants were randomly assigned to the experimental group (VIMT, n = 33) or active control group (n = 33). The VIMT program used the CogniPlus (includes four training modules). Both groups attended 45 min sessions 3 times per week, a total of 36 sessions. The primary outcome was working memory; secondary outcomes were immediate memory, delayed memory, subjective memory complaints and global cognitive function. All variables were measured at pre-test, post-test, and 3-month follow-up.
Results: between group, the effect of working memory adjusted mean difference by 1.75 (95% CI: 0.56 to 2.94; $P < 0.01$) at post-test. The results were analysed by a generalised estimating equation, which indicated that VIMT group significantly improved working memory at post-test ($P = 0.01$) relative to the active control group.
Conclusions: the applied VIMT program can enable older adults with MCI to maintain their working memory and reduce the rate of cognitive deterioration.
Trial registration: This trial was registered on ClinicalTrials.gov (no.: NCT02462135).

Keywords

Memory training, mild cognitive impairment, working memory, randomised controlled trial, older people

Key points

- Memory impairment is the most easily detected symptom of cognitive changes in individuals.
- Memory is thus a critical clinical representation of cognitive function decline.
- Memory training, a theory-based method that entails providing adequate brain stimuli and boosting cognitive plasticity.
- This study examined whether virtual interactive working memory training (VIMT) program influence memory in older adults with mild cognitive impairment (MCI).
- VIMT program may be effective for improving working memory in older adults with MCI.

Introduction

The risk of dementia is higher in older adults with Mild cognitive impairment (MCI) than in the general population, and the rate of conversion of MCI to dementia is estimated at 5–20% [1]. Memory impairment is the most easily detected symptom of cognitive changes; thus, memory is a critical clinical representation of cognitive function decline [2].

Working memory is thought to be heavily dependent on attention-based processes and/or the storage to carry out tasks, and that's been known generally considered a gateway between short-term memory and long-term memory [3, 4]. Immediate memory refers to the recall of information immediately after presentation and it is mainly used for measuring short-term memory. Delayed memory refers to the recall of material sometime after its presentation and is usually used for measuring long-term memory. Studies suggest that the risk of MCI and dementia in older adults with subjective memory complaints is 4.5 times higher than in those without such complaints; subjective memory complaints are also reported to be significantly correlated with memory performance and global cognitive function [5–7].

Virtual interactive working memory training (VIMT) is relatively novel and scalable intervention that aims to maintain memory in older adults. VIMT program is by means of training programs that simulate real-life situations, helps subjects to integrate their progress into everyday life using a multimedia approach. VIMT, typically without explicit teaching of memory or problem-solving strategies, which distinguish this training modus from other approaches for memory intervention. Recent meta-analyses of randomised controlled trials of memory intervention have found moderate effect sizes on cognition/memory in older adults [8–10]. A previous study indicated that 15–20% of older adults with MCI showed improvements in cognitive function or effective reductions in their risk of deteriorating cognitive function after receiving cognitive-related interventions performed 1–2 years after MCI development [1].

Despite evidence that memory training is useful for deferring declines in memory function, previous studies have mostly recruited healthy older adults and not older adults with MCI. Furthermore, only 37% of previous memory training studies were clinical trials and some did not provide detailed information regarding their randomisation and blinding [11–13].The effect of memory training on specific memory functions has not been adequately discussed. The present single-blind randomised clinical trial was designed as an intervention study. The objective of this study was to examine the effects of a virtual interactive working memory training (VIMT) program on working memory, immediate memory, delayed memory, subjective memory complaints, and global cognitive function in older adults with MCI compared to an active control group.

Methodology

Study design

This study applied a randomised, single-blind, two-arm parallel-group design to examine changes in working memory, immediate memory, delayed memory, subjective memory complaints, and global cognitive function in post-test and 3-month follow-up between the two interventions. The Regional Ethics Review Board of Taipei Medical University's Joint Institutional Review Board approved this study (approval no.:201301045).

Participants

Older adults living in retirement homes, retirement institutions, or retirement communities were recruited and enroled as participants. All data were collected between August 2013 and July 2016. Inclusion criteria were: (1) self-reported subjective memory complaints; (2) detection of significant memory impairment; (3) assessments of cognitive function using the Montreal Cognitive Assessment (MoCA) (At an optimal cut-off of below 23 for MCI and below 17 for dementia) [14, 15] and (4) ability to perform activities of daily living independently (assessment using the Basic activities of daily living [BADL] and Instrumental activities of daily living [IADL]). Exclusion criteria were: (1) diagnosis of dementia; (2) severe mental disease or behavioural problems; (3) rapid decline in cognitive or physical function; (4) severe sensory function or communicative impairment; and (5) receipt of related cognition or memory training in the preceding year. Before the screening, subjects were informed of the study goals and methods, and subjects who agreed to participate signed the study consent forms. After providing informed consent, participants were randomly assigned to either the experimental group (VIMT) or the active control group (Passive information activities [PIA]).

Randomisation, allocation concealment and blinding

The independent investigator generated a table of random numbers using a computer and used block randomisation (block size: 4), and placed the group assignment files in sequentially numbered opaque sealed envelopes (SNOSE) taken to conceal the sequence until interventions were assigned (allocation ratio = 1:1). Participants were informed beforehand that there were two intervention measures, they were not being able to determine whether they were randomly assigned to the VIMT group or the PIA group. The participants were not blinded, i.e. they knew what group they were allocated to and what treatment they were receiving. The assessors cannot discuss any study information related to the participants with the therapists, and they do not know which participants are receiving a genuine treatment. The assessors only responsible for collecting data during the study. All were kept blindness about which group participants are in, until the data-collection phase of the end.

Sample size calculation

Sample size was estimated using G-Power statistics software [16]. Participants were assigned either to the VIMT group or the PIA group (a = 0.05, power = 0.90, effect size = 0.45, drop-out rate = 21%) [17, 18]. Hence, oversampling was performed to enrol 62 participants with MCI (i.e. 31 participants per group).

Interventions

The VIMT program was used as an intervention in the present study. The VIMT program measures performance using CogniPlus software (Schuhfried GmbH, Vienna, Austria), which is a theory-based and scientifically-verified intelligent interaction system designed for training cognitive function. The training content was designed according to the working memory model [3, 4].The experimental group was subjected to a 45 min session 3 times per week for 12 weeks, for a total of 36 sessions. The training programmes were implemented in an individual form. Each type of working memory training was conducted over nine sessions. The four working memory training modules applied in this study are as follows:

(1) Updating—visual memory task: emphasises the training of the visual cache in the visual–spatial sketchpad. It is used to train the working memory monitoring function and improve the ability to retain information while continuously updating it. (2) Spatial encoding memory task: used to train and improve monitoring processes and spatial coding in the visual–spatial sketchpad. It is a basic working memory mechanism that involves cognitive function control and coordination; it is regarded as the basis for complex cognitive processes. (3) Rehearsal—visuospatial training task: emphasises the training of the visual scribe in the visual–spatial sketchpad. (4) Updating—spatial memory task: used to train and improve the update function, a basic working memory mechanism that involves control and target stimulus repositioning. In this training module, three tasks must be completed, namely running memory, keep-track, and n-back. The four working memory training modules were performed in sequence (see the training content of the VIMT program in Appendix 1 of the online supplementary data). VIMT modules was used to improve rehearsal abilities and assist trainees to practice retrieval and re-encoding under self-control and attentional control.

The active control group in the PIA intervention using a tablet computer. The contents of the control training program included reading online e-books and playing online games, such as puzzles, spot the differences, etc.…, and the training frequency was being identical (45 min sessions 3 times per week for 12 weeks, a total of 36 sessions) [19].

Outcome measures

The primary outcome was the working memory. Working memory was measured using the digit span (DS)—backward task to assess working memory [20]. Secondary outcomes were immediate memory, delayed memory, subjective memory complaints, and global cognitive function. The immediate memory and delayed memory scores were calculated using the Wechsler Memory Scale—Third Edition (WMS-III) [20]. Immediate memory comprises immediate memory, auditory immediate memory, and visual immediate memory. Delayed memory comprises delayed memory, auditory delayed memory, and visual delayed memory. All scores were derived from age-standardised scores in the individual scales. Subjective memory complaints, which were determined using the Multifactorial Memory Questionnaire (MMQ). The MMQ consists of three subtests (ability, strategy, and contentment) [21]. Global cognitive function was evaluated using the Mini-Mental Status Examination (MMSE) [22] and the MoCA [14, 15].

Statistical analysis

All analyses were performed according to the intention-to-treat (ITT) principle. Data from all randomly-assigned participants were included in the final statistical analysis [23, 24] and analysed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA). Each participant had three time point measures: pre-test, post-test,and three-month follow-up. The data were analysed using independent t-tests and Chi-square tests. For all outcome measures, between-group differences in mean changes from baseline to each time point (post-test and three-month follow-up) were analysed using generalised estimating equations (GEEs) modelling with Least—Significant Difference (LSD) post hoc tests. Intervention effectiveness was repeatedly measured using GEEs analysis, which were used to identify time-dependent changes in outcome variables by examining the effects of VIMT on MCI and comparing the differences between the two groups (Repeated measures effect, model: group, time, group x time interaction). GEEs analysis provide estimations of changes from baseline. Missing data will use multiple imputation (MI) of imputation to estimate. The significance level was < 0.05 (two-tailed).

Table 1. Demographic characteristics and categorical data (N = 66)

Variable	Total (N = 66)	VIMT (n = 33)	PIA (n = 33)
Age, mean ± SD	78.5 ± 7.6	75.4 ± 6.6	81.7 ± 7.2
Sex, n (%)			
Male	14(21.2)	8(24.2)	6(18.2)
Female	52(78.8)	25(75.8)	27(81.8)
Marital status, n (%)			
Single	4(6.1)	2(6.1)	2(6.1)
Married	22(33.3)	14(42.4)	8(24.2)
Widowed	36(54.5)	15(45.5)	21(63.6)
Divorced	4(6.1)	2(6.1)	2(6.1)
Education, n (%)			
Elementary school	17(25.7)	7(21.2)	10(30.3)
Junior high school	8(12.1)	3(9.1)	5(15.2)
Senior high school	18(27.3)	9(27.3)	9(27.3)
College	23(34.8)	14(42.4)	9(27.3)
BADL, mean ± SD	99.3 ± 7.6	98.8 ± 5.5	99.9 ± 0.9
IADL, mean ± SD	7.8 ± 0.9	7.6 ± 1.2	8.0 ± 0.2
MMSE, mean ± SD	27.0 ± 2.3	27.4 ± 2.1	26.6 ± 2.4
MOCA, mean ± SD	23.9 ± 4.1	24.6 ± 4.1	23.2 ± 4.0
GDS-SF, mean ± SD	2.4 ± 2.8	1.8 ± 2.7	3.0 ± 2.9

VIMT, Virtual interactive working memory training; PIA, Passive information activities; SD, Standard deviation; BADL, Basic activities of daily living; IADL, Instrumental activities of daily living; MMSE, Mini-Mental Status Examination; MoCA, the Montreal Cognitive Assessment; GDS-SF, the Geriatric Depression Scale-short form.
[a]Independent t-test.
[b]Chi-square test

Results

Sample characteristics

Ninety-three adults participated in this study. Participants were randomly assigned to the VIMT group (n = 33) or PIA group (n = 33). The difference of age in baseline was adjusted using multivariate generalised linear models. No significant differences were detected in other baseline data (Table 1). The total dropout rate of this study was 4.5%, 1 (0.03%) participant from the VIMT group and 2 (0.06%) participants from the PIA group had dropped out. The reasons for dropping out were leaving the residence and hospitalisation (Fig 1). None of the participants exhibited adverse reactions during the training.

Outcome measures

Table 2 presents the results of all outcome measures at pre-test, post-test, and three-month follow-up. At post-test, the VIMT group showed statistically significant difference compared to the PIA group on working memory, subjective memory complaints (MMQ Strategy), and globe cognitive function (MMSE); At three-month follow-up, the VIMT group is statistically significant different from the PIA group on the globe cognitive function (MoCA) (difference = 2.27 points, 95% CI = 0.18 to 4.37, P = 0.03) (Table 2).

The effectiveness of the interventions were observed in the GEE analysis results, where a significant time × group interaction effect was discerned in the effect of the VIMT program on post-test DS scores (P = 0.01), which were superior to those of the PIA group (Appendix 2 , available in *Age and Ageing* online). Therefore, VIMT engendered significant improvements in working memory. The secondary outcome measures included: immediate memory, delayed memory,

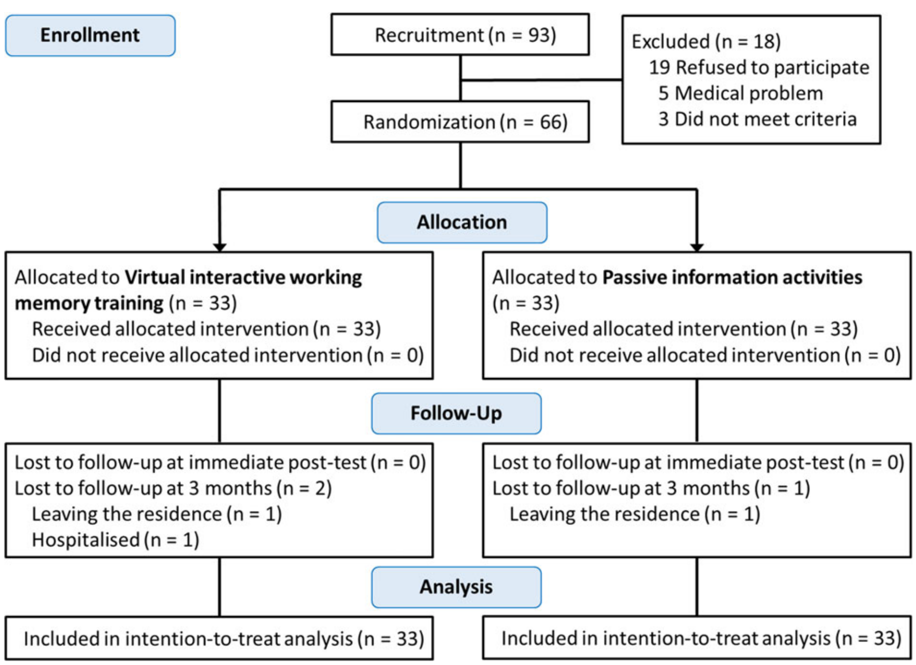

Figure 1 Participant enrolment according to the CONSORT 2010 flow diagram.

Table 2. ITT repeated measures analysis between groups in outcome variables at pre-test, post-test, and 3-month follow-up (N = 66).

Outcome variables	Pre-test (Baseline)				Post-test							3 months after training						
	VIMT		PIA		VIMT		PIA		Adjusted MD[a]	95%CI	p-value[b]	VIMT		PIA		Adjusted MD[a]	95%CI	p-value[b]
	Mean	SD	Mean	SD	Mean	SD	Mean	SD				Mean	SD	Mean	SD			
Primary outcome																		
Working memory																		
DS-Backward	6.03	2.48	5.67	1.98	7.12	2.88	5.03	2.22	1.75	0.56 to 2.94	**<0.01**	6.57	3.35	5.22	1.88	0.97	−0.23 to 2.17	0.11
Secondary outcomes																		
Immediate memory index																		
Immediate memory	46.82	9.89	43.06	8.67	51.09	11.25	48.27	9.99	1.18	−4.18 to 6.53	0.67	54.70	10.51	51.66	10.89	1.91	−3.71 to 7.54	0.51
Auditory immediate	23.03	6.20	21.33	6.81	25.15	6.45	22.58	5.35	2.84	−0.13 to 5.82	0.06	27.50	6.21	25.09	6.12	2.91	−0.34 to 6.16	0.08
Visual immediate	23.82	5.39	22.97	4.61	26.21	6.02	25.70	5.44	−0.89	−3.88 to 2.09	0.56	27.83	5.95	26.53	5.84	0.15	−3.00 to 3.30	0.93
Delayed memory index																		
Delayed memory	58.73	10.85	55.18	13.57	63.97	11.12	61.48	12.05	1.41	−4.99 to 7.81	0.67	67.87	12.14	63.75	12.94	3.06	−3.87 to 9.98	0.39
Auditory delayed	23.09	6.44	22.48	6.71	25.82	5.55	23.64	6.02	2.61	−0.39 to 5.61	0.09	27.10	5.97	25.13	6.57	2.61	−0.69 to 5.91	0.12
Visual delayed	23.64	4.72	23.55	4.20	25.64	4.99	25.70	5.32	−1.07	−3.90 to 1.77	0.46	27.57	5.67	26.03	5.65	0.72	−2.33 to 3.78	0.64
Subjective memory complaints																		
MMQ Ability	55.22	13.31	58.55	13.52	56.61	11.28	60.27	12.76	−2.35	−8.61 to 3.91	0.46	59.03	12.90	59.81	11.12	−0.17	−6.83 to 6.48	0.96
MMQ Strategy	28.59	12.52	20.67	11.64	26.73	12.35	18.00	10.60	8.77	3.10 to 14.44	**<0.01**	25.94	14.22	21.41	11.18	4.56	−1.93 to 11.05	0.17
MMQ- Contentment	38.94	5.82	38.61	5.03	37.85	5.23	36.64	4.97	1.37	−1.24 to 3.98	0.30	37.03	6.18	39.13	19.75	−1.86	−8.99 to 5.27	0.61
Global cognitive function																		
MMSE	27.36	2.07	26.61	2.41	27.79	2.27	26.39	3.00	1.35	0.03 to 2.67	**<0.05**	27.58	2.26	26.29	3.25	1.29	−0.13 to 2.71	0.07
MoCA	24.64	4.09	23.24	3.95	25.85	3.46	24.18	4.30	1.34	−0.61 to 3.29	0.18	25.81	3.57	23.41	4.63	2.27	0.18 to 4.37	**0.03**

VIMT, Virtual interactive working memory training; PIA, Passive information activities; M, Mean; SD, Standard deviation; MD, Mean difference (Group difference-reference group: VIMT); CI, Confidence intervals; DS, Digit span; MMQ, Multifactorial Memory Questionnaire; MMSE, Mini-Mental Status Examination; MoCA, Montreal Cognitive Assessment.

Statistically significant values are highlighted in bold ($P < 0.05$).

[a]Adjusted for VIMT group, age and baseline score.

[b]p-value for adjusted mean difference between two groups.

subjective memory complaints and global cognitive function. The GEE analysis results did not show any effect of the VIMT program on all secondary outcomes at post-test and three-month-follow-up (Appendix 2 and 3, available in *Age and Ageing* online), but the means of these variables exhibited short-term stable trends and no signs of decline (Table 2).

Discussion

Working memory training relies on memory processes and strategies to strengthen recall capacity, which can be trained via two general mechanisms: enhanced working memory capacity or efficiency. Multiple factors may influence mechanisms mediating transfer effects and success of training interventions, such as the training program and individual differences [10, 11, 25]. Working memory is crucial for processing daily needs, particularly those needs pertaining to information retention, representations of cognitive processing, and task implementation, such as remembering a phone number or understanding long and difficult sentences. DS-backward exhibited a higher correlation with working memory compared with DS-forward, as DS-backward requires individuals to recall a sequence in reverse order while coding the numbers that are heard, which is a relatively difficult task. Immediate and delayed memory were found to be highly correlated with cognitive impairment; delayed memory was also confirmed as an effective predictor of MCI progression to dementia. The results of the present study are consistent with previous findings, which concluded that memory training have significant effects in older adults, suggesting that cognitive plasticity is preserved in old age [26–28]. However, participants of PIA group were significantly older in this study, they may have exhibited lesser training gains and cognitive plasticity compared to VIMT group.

In accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement, this rigorously designed study showed that working memory training (i.e. VIMT) can enable older adults with MCI to maintain their cognitive or memory status and reduce the rate of cognitive deterioration. By strengthening working memory, can help individuals memorise information more easily (e.g. phone numbers) when they are provided with information stimuli in daily settings. Older adults with MCI can further motivate the continued acquisition of memory function and the use of new memory strategies by the training program. However, the study was followed only three-month follow-up, future studies were required with long term follow-up and more outcome measures of transfer effect, i.e. function, mood, quality of life, other cognitive domains such as: visuospatial abilities, attention etc…, which further verifies the prevented progression to dementia and reduction of hazards in daily life. Booster sessions can be seen as one of the strategies to sustain the long-term effects of training. The main contributions of this study are as follows. First, this is the first study in Chinese population to develop a systematic training model (i.e. the VIMT program) specifically for older adults with MCI. Training software was applied to offer specialised training conditions depending on each participant's characteristics and enabled the researcher to immediately and objectively compare data using real-time feedback. Second, VIMT program is more cost-effective and personalised than traditional memory training. It is easy to operate. Subjects are required to press one button only to respond in the training procedure. Thus, the training doesn't operate difficult for older adults to accomplish and adapts task difficulty to individual performance. Finally, this study applied a wide range of memory-related outcome measures for a detailed analysis of the effectiveness of intervention. This study has several limitations. The working memory training may benefit older adults, but regarding training and transfer effects in older adults may be more complex and restricted compared with younger participants. Although an effective sample size was used in the study, the sample size should be further increased to examine the dose–response effect of training and transfer effects (e.g. training sessions, duration) [29, 30]. In addition, lack of blinding of participants in this study. Therefore, we were recommended that the groups are treated as equally possible, such as provided the training frequency was being identical.

The systematic training model (the VIMT program) applied in this study can be applied in institutions or communities and incorporated into regular activities and long-term programmes to provide comprehensive care services to help delay the progression of cognitive and memory loss in older adults. Further research is required to confirm these findings and establish if there is a clinically worthwhile benefit.

Supplementary Data: Supplementary data are available at *Age and Ageing* online.

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Declaration of Conflict of Interest: None.

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