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Computerized Cognitive Training Enhances Episodic Memory by Down-Modulating Posterior Cingulate-Precuneus Connectivity in Older Persons With Mild Cognitive Impairment: A Randomized Controlled Trial

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ABSTRACT

Objective: *The neural mechanisms underlying the beneficial effects of a computerized cognitive training (CCT) program for improving episodic memory in older persons with mild cognitive impairment (MCI) remain unclear. This study aimed to use both functional and structural brain changes to elucidate the treatment effects of CCT on enhancing episodic memory.* ***Design, setting, and participants:*** *Single-blinded, multicenter randomized controlled trial on 60 older adults with MCI in Fuzhou, China.* ***Intervention:*** *Participants were randomly assigned to either an 8-week 24-hour CCT program or a health education program as the control.* ***Measurements:*** *Clinical outcomes included changes in scores on the immediate and/or delayed recall subtests of the Chinese auditory verbal learning test (CAVLT) and rey complex figure test (CFT),*

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and changes in gray matter volume and the functional connectivity of the posterior cingulate cortex (PCC) and hippocampus in the Papez circuit on magnetic resonance imaging. ***Results:*** *Significant group-by-time effects showed greater improvements in both immediate and delayed recall scores of CAVLT and delayed recall scores of Rey CFT in participants receiving the CCT program compared to those in the health education program. Among the CCT participants, seed-based analyses revealed decreases in functional connectivity of the PCC and hippocampus with neural substrates in the parietal and occipital regions. The decreased PCC and precuneus connectivity were found to mediate patients' improvements in immediate recall function.* ***Conclusion:*** *An 8-week CCT program was effective for improving episodic memory in older individuals with MCI. The decrease in connectivity originating from the PCC and hippocampus is suggestive of potential plastic changes in the Papez circuit, which could have alleviated the age-related compensatory mechanism. The findings of this study also shed light on expanding the content and extending the frequency and duration of the CCT program in future studies.* (Am J Geriatr Psychiatry 2023; 31:820–832)

Highlights

- **What is the primary question addressed by this study?**
  How does computerized cognitive training (CCT) improve the episodic memory performance related to the Papez circuit in individuals with mild cognitive impairment?
- **What is the main finding of this study?**
  In this randomized trial that included 60 older persons with mild cognitive impairment, the CCT improved their episodic memory performances, which were mediated by the decrement of the functional connectivity between the posterior cingulate gyrus and precuneus in the Papez circuit.
- **What is the meaning of the finding?**
  This trial may provide theoretical insight into the clinical application and rehabilitation mechanism of CCT on episodic memory improvements.

INTRODUCTION

As the aging population grows, age-related degeneration such as mild cognitive impairment (MCI) and dementia has become a major societal concern.[1,2] Unlike patients with dementia, individuals with MCI are characterized by isolated cognitive function losses with a milder severity level.[3–5] Episodic memory has been found to be sensitive to age-related neurodegeneration.[6] Episodic memory is the ability to learn, store, and retrieve information and events that occurred in daily living.[7] Previous studies revealed negative relationships between episodic memory performance and cognitive aging.[8,9] Therefore, episodic memory decline is a main concern in the management of individuals with MCI.

Studies have shown promising treatment effects of CCT on individuals with MCI. For instance, meta-analyses of studies on CCT revealed that individuals with MCI had improved global cognitive function, memory, and attention after the interventions.[10,11] The most frequent dosage of the CCT in 17 trials cited in one paper was 24 sessions.[10] The duration of the 24-session training ranged from 8 to 24 weeks.[12,13] Other studies suggested that, among cognitive deficits, loss of episodic memory is common among individuals with MCI.[14] In addition, the positive effects of cognitive training on improving episodic memory were found to compensate for other cognitive domain deficits in individuals with MCI or mild-to-moderate dementia.[15,16] However, the neural mechanism underlying the treatment effects of CCT on episodic memory is still unclear.

Converging evidence suggests that the Papez circuit plays a major role in subserving episodic memory.[17] The Papez circuit is primarily composed of neural substrates from the limbic system, including the hippocampus, anterior thalamic nucleus, mammillary bodies, and posterior cingulate cortex (PCC).[18-20] These Papez circuit nodes are connected to act upon the neocortical sites to subserve the encoding and retrieval processes of the episodic memory.[21] Damages to nodes of the Papez circuit were reported to impact on episodic memory performance.[22,23] In particular, the PCC and hippocampus were found to be structurally connected within the circuit.[24−28] More importantly, patients with MCI showed significant aversive changes in the structural integrity[29] or functional connectivity[30,31] of the PCC and hippocampus nodes. Hyper-functional connectivity of the PCC with the precuneus was positively associated with participants' low episodic memory performance in MCI due to suspected Alzheimer's disease, especially for the amnestic MCI type.[30] Decreased gray matter volume and increased functional connectivity of the hippocampus to more diffuse areas of the brain were negatively associated with participants' episodic memory performance.[29,31] Therefore, the structure and function of the PCC and hippocampus would be the key candidates in this study to reflect the changes in episodic memory of older adults with MCI.

This study aimed to elucidate the neural process enhancement resulting from a group of older adults with MCI in a randomized controlled trial of an 8-week multimodal CCT program. We hypothesized that participants who complete the standardized training program, when compared with those in the control group, would show significant improvements in episodic memory measures. We further hypothesized that the improvements in episodic memory measures would be associates with an increase in the gray matter volume of the hippocampus and PCC and a decrease in the hyperfunctional connectivity among the hippocampus, PCC, and their related nodes within the Papez circuit.

METHOD

Study Design and Registrations

This study employed a parallel-group, single-blinded, three-center randomized controlled trial design in accordance with the CONSORT statement. Ethics of the trial was approved by the ethical committees of the participating hospitals (2020QX-001-02, 2020-054-02, SPHFJP-L2020001-02). The trial was registered in the Chinese Clinical Trial Registry in June 2020 (ChiCTR2000034012).

Participants

Out-patients diagnosed with MCI in the memory clinics of three hospitals located in Fuzhou were invited to participate in the screening tests. Regarding the method of recruitment, the study was advertised on the websites of the hospitals and on notice boards in the memory clinics. The patients who intended to participate were explained the purpose of the study, and their informed consent was obtained, before completing the screening tests. Those who fulfilled the inclusion criteria were enrolled in the study. Physicians working in the memory clinics were responsible for diagnosing MCI in the participants according to Petersen's criteria published in 2018.[1] The inclusion criteria for the participants were: 50−85 years old; score less than or equal to 25 (£ 24 for those with less than 12 years of education) on the Chinese version of the Montreal cognitive assessment (MoCA)[32]; score of 2 or 3 on the global deterioration scale (GDS)[33]; right-handedness; and no contraindications for magnetic resonance imaging (MRI). The exclusion criteria were as follows: current or history of dementia or other psychiatric diseases; score greater than 10 on the Hamilton depression scale (HAMD) for presence of depressive mood[34]; score greater than or equal to 5 on the Hachinski ischemic scale[35] for identifying possible vascular-related causes; current or history of alcohol or drug abuse; and on medication within the last 2 weeks that may affect cognitive functions.

Randomization and Masking

We randomly assigned eligible participants into the training group (received CCT program) and the control group (received health education program) in a ratio of 1:1. Participant group allocation was conducted by a research team member who was not involved in the intervention and assessment, using a computer-generated sequence of blocks of four. In this study, it was not possible to blind the participants because the contents of the experimental and control

interventions had to be explained to them before randomization. The single blinding was applied to the clinicians who conducted the baseline and postprogram assessments, as they did not have knowledge about the group assignment and interventions received by the participants. Thus, potential assessor biases were minimized in this trial.

Procedures

Baseline assessments were conducted within 1 week before the participants commenced the interventions. Postintervention assessments were completed within 1 week after the last training session in the 8th week. Cognitive tests and structural and functional magnetic resonance imaging (MRI) were conducted during both assessments by research team members who did not have knowledge about the group assignment and interventions received by the participants.

Computerized Cognitive Training Program (CCT)

The CCT used in this study was the cognitive assessment and rehabilitation training machine (called the System) (No. YJRZ-LJ-01), which has been approved by the Chinese FDA (No. 20212190249) (https://www.nmpa.gov.cn/datasearch/search-result.html). The CCT consists of 11 modules involving training tasks that cover various cognitive domains common to neurodegeneration, such as attention, working memory, and response speed. Details of the names, content descriptions, and cognitive domains of the training modules can be found in Table 1 of Supplementary Material. In general, the contents of the modules range from simple tasks tapping basic cognitive functions to complex tasks tapping advanced cognitive functions. For instance, module #1 is "Warm Up" involves basic visual attention and simple response task design; while module #11 is "Mental Rotation" involves advanced attention control and working memory for image transformation. The training program consisted of three 1-hour sessions per week for 8 weeks, giving a total of 24 hours. All sessions were conducted at the department of rehabilitation in the hospital from which the participant was recruited. In each session, a research team clinician was responsible for preparing the participant to engage in the CCT according to a personalized task protocol (see below). All clinicians were occupational therapists and received training on operating the software and hardware of the System. The participant sat in front of a computer screen of the System, located in a quiet corner, on which the task was displayed. Each participant was explained the operation of the System in the first session. The participant was required to pay attention to the stimuli displayed and make appropriate responses through a mouse-like device of the System. The progression of the tasks/modules was automated according to the protocol. The clinician ensured that the participant was comfortable throughout the training session and offered rest breaks whenever necessary.

Participants' CCT program was based on a personalized task protocol designed by the research team. The purpose of the personalization was to increase the sense of relevance to enhance the participant's motivation to engage in the training. The personalization regime involved organizing the tasks in a sequence according to the participant's cognitive deficits based on the less than full MoCA item scores at

TABLE 1. Demographic Characteristics of Participants in the Training and Control Groups, and Their Comparisons (Mean [SD]/Median [P25, P75])

Variables	Training Group n = 27	Control Group n = 26	t/Z/χ^2	p Value
Age (year)[a]	68 (63, 74)	65.5 (61.5, 68.5)	−1.481	0.139
Sex (F/M)[b]	20/7	21/5	0.339	0.560
Education (year)[a]	9 (7, 10)	9 (8, 12)	1.280	0.227
BMI (kg/m^2)[c]	23.60 (3.46)	22.80 (2.65)	0.948	0.347
Diabetes (y/n[b]	4/23	7/19	1.181	0.277
Hypertension (y/n)[b]	11/16	5/21	2.908	0.088
HAMD[a]	2 (0, 3)	1.5 (0, 2)	−0.874	0.382
IADLs[a]	23 (22, 23)	23 (22, 23)	−0.249	0.803

[a] Variables of continuous data in non-normal distribution (age, education year, and scores of HAMD and IADLs) were examined by Mann-Whitney U test.
[b] Variables of categorical data (sex, diagnoses of Diabetes and Hypertension) were examined by Chi-square test (all df = 1).
[c] Variable of continuous data in normal distribution (BMI) was examined by t-test (df = 51).

baseline. Task demands in the 11 modules were mapped to the MoCA items with reference to the mapping scheme described in a previous study[36] (Table 1, Supplementary Material). Modules that were associated with the MoCA-based deficits were collated and assigned to the participants earlier in the training session than other tasks. The delivery of these modules followed the numbering of the CCT modules, that is, from relatively basic cognition functions and simple tasks to relatively advanced cognition functions and complex tasks. Tasks in one module were organized in six to nine difficulty levels. For instance, the #8 "working memory" module employs the n-back paradigm. Module #8 were assigned to the participants for less than full scores on the MoCA's "Digit Backward" (1/1), "7s Subtraction" (3/3), or "Orientation" (6/6). This module required the participants to performing the following: "compare stimulus that just appeared with one previous designated stimulus, and press a key on the keyboard to indicate a match between the two stimuli" (Supplementary Material, Table 1). This module has nine difficulty levels, graded according to the nth back and complexity of the objects, and the similarity of the outlook between the stimulus and matched objects. Levels 1−3 were one-back, with increasing complexity and similarity of the stimulus and matched objects. In contrast, levels 7−9 were three-back, with increasing object complexity and similarity. For each module assigned, the participant began with the easiest level, and then progressed to the next levels according to the performance achieved in the previous level. The rules of progression were based on the accuracy rate achieved within the same level: greater than or equal to 80%: advances from a lower to a higher level; 60%−79%: repeats the same level; and less than 60%: retrack from a higher to a lower level. The accurate rate of each participant within one level in one task was computed by the system right after the task completion. The adaptive algorithm of the System used the accurate rate to direct the assignment of the task. The progression of tasks across different difficulty levels and across modules was automated in the System.

Health Education Program as Control

The health education program consisted of eight 1-hour weekly sessions for participants assigned to the control group. The content of the health education program was created based on the guidelines for the prevention of Alzheimer's Disease published by Barnard et al.[37] in 2014. The content consisted of information on the risk factors of cognitive impairment or dementia and prevention strategies covering dietary and lifestyle measures. The participants attended face-to-face education courses in another location within the department of rehabilitation. Two clinicians in the research team, who were occupational therapists in training and were not involved in the CCT program, conducted the control training. The clinicians received training on the contents and educational methods. The reason for providing the health education program was to maintain contact with the participants in order to minimize their attrition in the post-intervention assessments. The participants were reminded not to engage in cognitive training regardless of whether it was delivered face-to-face or through a computer.

Outcome Measures

The primary outcome measures were two clinical measures of episodic memory, including the immediate and delayed recall subtests of the Chinese Version Auditory Verbal Learning Test (CAVLT) and the delayed recall subtest of the Chinese Version Rey-Osterrieth Complex Figure Test (Rey CFT). These subtests assess the verbal and non-verbal episodic memory, respectively.[38,39] In the CAVLT immediate and delayed recall subtests, participants are required to learn and recall 15 words in the first instance and then recall the same words after 20 minutes of delay. In the Chinese Version Rey CFT, the participants are required to copy-draw a figure, and after 20 minutes, to draw the figure based on their recall. The secondary outcome measures were signals from the MRI scan, including the gray matter volume (GMV) of the PCC and hippocampus and their functional connectivity.

MRI Data

MRI Data Collection

The MRI data were obtained using the Siemens Prisma 3.0 Tesla system (Erlangen, Germany) located in one of the participating hospitals. The T1 structural images and resting-state functional images were acquired using MPRAGE T1-weighted sequence and Gradient-echo EPI sequence. The T1 sequence parameters were: 256 × 256 matrix size, 192 contiguous

slices with 1 mm slice thickness, 2,530 ms repetition time, 2.51 ms echo time, 7 degrees flip angle, field of view = 256 × 256 mm2, voxel size = 1.0 × 1.0 × 1.0 mm3. Parameters of the resting-state fMRI scan were: field of view = 224 mm × 224 mm2, voxel size = 3.5 × 3.5 × 3.5 mm3, 37 contiguous slices with 2 mm thickness, 2,000 ms repetition time, 30.0 ms echo time, 90 degrees flip angle, and 240 time points.

Gray Matter Volume

Volumetric analysis of the gray matter was performed using Statistical Parametric Mapping (SPM12) software (https://www.fil.ion.ucl.ac.uk/spm/).

Seed-Based Functional Connectivity

Resting-state functional MRI data were preprocessed by using SPM12 and DPABI (a toolbox for Data Processing & Analysis of Brain Imaging)[40] software through the following processes: removal of the 10 first time points, slice timing, realignment (Friston model, threshold was 3 mm transmission or 3 degrees rotation), regressing out covariates, normalization (Voxel size = 3 × 3 × 3 mm3), smoothening with a 6-mm full width at half maxima Gaussian kernel and temporally Filter (0.01-0.1Hz).

Statistical Analysis

Group differences in demographic characteristics at the baseline line were examined using the Chi-square test and t-test or Mann-Whitney U test. The CCT treatment effects were tested using a linear mixed model (LMM) on the primary outcomes, scores on the CAVLT and Rey CFT subtests, and the secondary outcomes, the GMVs of the PCC and hippocampus and their functional connectivity. The LMM generates the fixed and random effects of the Group, Time, and Group × Time, with age, gender, and years of education of the participants as covariates. Within-group comparisons were conducted using paired t-test or Wilcoxon test. Effect sizes of the CCT for participants in the training group, represented by Cohen's d value, were calculated according to the formula: $Cohen's\ d = \frac{Mean\ diff}{SD\ diff}$, where the numerator is the mean of the difference in scores (Mean diff), and the denominator is the standard deviation of the difference in scores (SD diff).[41] Partial correlation analysis was then performed, after controlling for age, gender, and years of education, to explore the associations between the changes in the primary and secondary outcomes that showed significant group-by-time effects. The significance level was set at a two-tailed P value of 0.05.

For the MRI data, a seed-based approach was performed to identify the alternation functional connectivity of the PCC and hippocampus. The regions of interest (ROIs) of these two neural substrates were defined using the WFU_Pickatlas software (www.fmri.wfubmc.edu).[42] Functional connectivity of the neural substrates was based on Pearson's correlation coefficients between the two ROIs and the whole brain. The treatment effects on the functional connectivity were tested with SPM12 and the thresholds were set as Voxel $p<0.005$ uncorrected and Cluster $p<0.05$ FDR corrected.

Second level analyses were conducted after a significant association was found between PCC precuneus functional connectivity and the CAVLT immediate recall subtest scores. Mediation models were constructed with the Group as an independent variable, changes in the CAVLT immediate recall subtest score as the dependent variable, and PCC_precuneus connectivity as the mediator variable, after controlling for age, gender, and years of education. The SPSS PROCESS macro software was used to test the indirect effect using the nonparametric bootstrapping procedure (5,000 times of bootstrapping), and the 95% confidence interval (CI) for the effect inference was obtained.

RESULTS

Participants' Characteristics

Between July 2020 and Dec 2021, 106 outpatients with MCI were invited for the screening, and 60 of them were eligible to participate in the study. Thirty participants were randomly assigned to the CCT, and 30 participants to the health education program as the control. Three participants (one in CCT and two in the control) dropped out due to refusal to complete the post-intervention MRI scan or residential relocation. All other participants completed the interventions. However, four participants were excluded from the data analyses due to over-threshold head-motions in the MRI scans (two in CCT and two in the control). The

TABLE 2. Summary of Participants' Results of the Mixed Linear Model Analysis and Within-Group Comparisons on the Primary and Secondary Clinical Outcomes of the Training Versus Control Groups

	Training Group					Control Group				
	Pre	Post	t/Z	*df*	p	Pre	Post	t/Z	*df*	p
CAVLT immediate recall	19.59 (5.20)	23.15 (4.90)	4.097	26	<0.001	21.08 (5.12)	21.54 (4.99)	0.666	25	0.512
CAVLT delayed recall	7.00 (4.00, 8.00)	9.00 (4.00, 10.00)	−2.772	-	0.004	6.46 (2.96)	6.15 (2.62)	-0.712	25	0.483
Rey CFT recall	12.78 (7.36)	17.00 (7.59)	3.672	26	0.001	16.04 (7.05)	16.46 (8.86)	0.491	25	0.628
GMV of PCC	0.2998 (0.0416)	0.3019 (0.0414)	1.513	26	0.142	0.3016 (0.2702, 0.3264)	0.3085 (0.2699,0.3287)	-0.140	-	0.889
GMV of Hippocampus	0.4028 (0.0406)	0.4074 (0.0381)	2.224	26	0.035	0.4251 (0.0405)	0.4276 (0.0393)	1.646	25	0.112

	Group Effects			Group × Time Effect				
	t	df	p	t	p	t	df	p
CAVLT immediate recall	2.256	67.222	0.027	−0.579	0.565	−2.773	51	0.008
CAVLT delayed recall	2.276	61.573	0.026	0.701	0.487	−2.727	51	0.009
Rey CFT recall	1.411	64.940	0.163	−0.404	0.688	−2.590	51	0.012
GMV of PCC	−0.394	48.975	0.695	−0.395	0.695	−0.755	51	0.454
GMV of Hippocampus	−1.318	49.540	0.194	−1.355	0.182	−0.816	51	0.418

Notes: Pre = Baseline, Post = Post-training. The data of neuropsychological tests was presented by mean (SD) or median (P25, P75) according to the normal distribution. Group, Time, and Group-by-Time effects were analyzed with linear mixed model (LMM). Within-group comparison (post minus pre) was tested with paired t-tests or Wilcoxon test according to the normal distribution.

final sample size that entered the analyses was 53 participants, with 27 in the CCT and 26 in the control group (Supplementary Material, Fig. 1). No significant differences were found in the demographic characteristics between the two groups (Table 1).

Primary Outcome Differences

The group-by-time effect was significant for score of the CAVLT immediate recall subtest score (LMM, t= -2.773, df=51, p = 0.008), CAVLT delayed recall subtest (LMM, t = -2.727, df = 51, p = 0.009), and Rey CFT recall subtest (LMM, t = -2.590, df = 51, p = 0.012) (Table 2, Fig. 1 A, B). Participants in the CCT group showed significant post-intervention improvements in the scores of the CAVLT immediate recall (paired t-test, t = 4.097, df = 26, p<0.001, Cohen's d = 0.789), CAVLT delayed recall (Wilcoxon test, Z = -2.772, p = 0.004, Cohen's d = 0.603), and Rey CFT recall tests (paired t-test, t = 3.672, df = 26, p = 0.001, Cohen's d = 0.707), which was not observed among those in the control group (p>0.05) (Table 2, Fig. 1A, B).

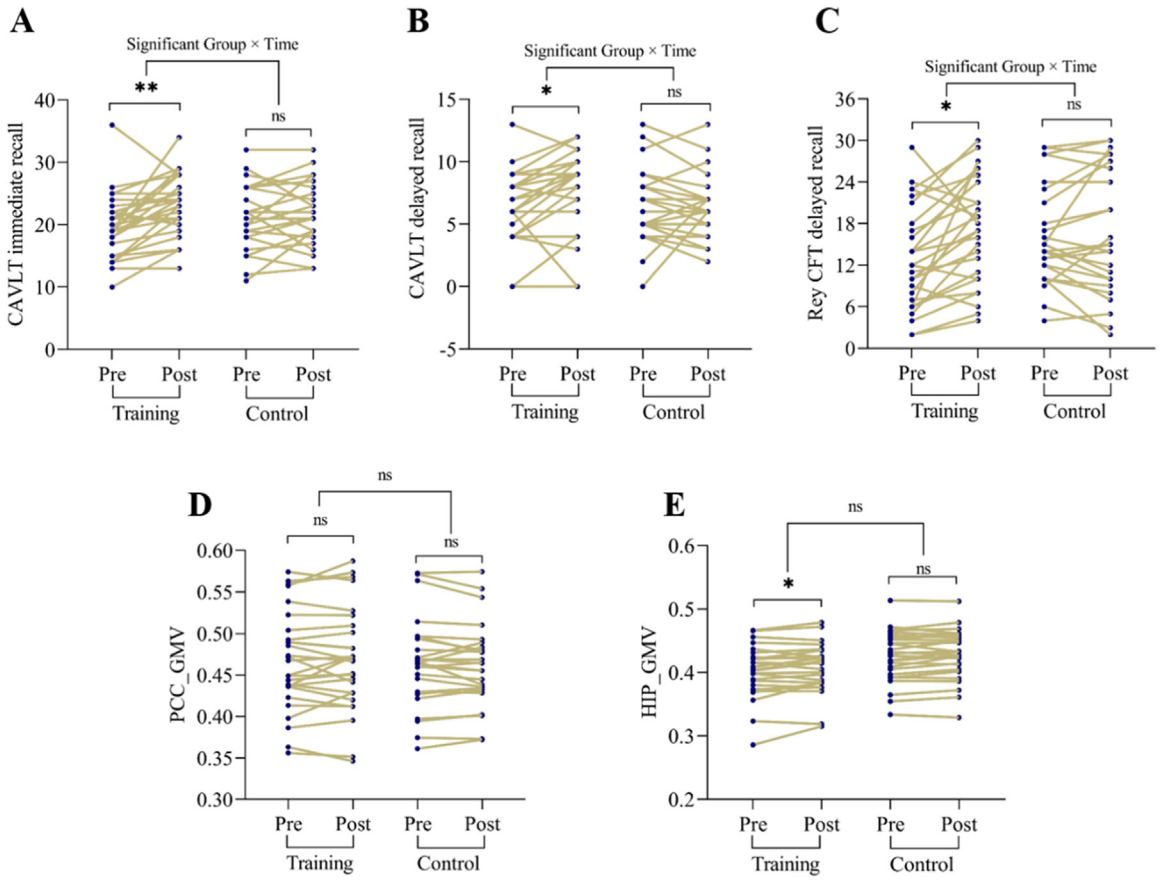
Secondary Outcome Differences

No significant group, time, and group-by-time effects were found in the GMV of the PCC and hippocampus (p>0.05) (Table 2, Fig. 2C, D). However, there were significant changes in the hippocampus GMV in the CCT participants (t = 2.224, df = 26, p = 0.035, Cohen's d = 0.430) compared to the control counterparts (t = 1.646, df = 25, p = 0.112).

Functional Connectivity

Two significant changes in functional connectivity were observed among participants in the CCT group but not in the control group. First, significant decreases in functional connectivity were found between the ROIs defined at the PCC and those at the right precuneus (t-test, voxel number=162, t = -4.067, df = 51, cluster P_{FDR} = 0.033) and left angular gyrus (t-test, voxel number = 244, t = -3.997, df = 51, cluster P_{FDR} = 0.012) (Table 3, Fig. 2A). Second, the ROIs defined at the hippocampus showed significant decreases in functional connectivity with the right inferior occipital lobe (t-test, voxel number = 371, t = -4.162, df = 51, cluster P_{FDR} < 0.001) and the left inferior parietal lobe (t-test, voxel number = 578, t = -4.030, df = 51, cluster P_{FDR} < 0.001) (Table 3, Fig. 2B). Significant negative correlations were revealed between the changes in PCC_precuneus connectivity and the change in scores on the CAVLT immediate recall subtest (r = -0.438, df = 22, p = 0.032) after controlling age, gender, and years of education. No other

FIGURE 1. Results of LMM and within-group comparisons of the scores on the primary outcome measures, including CAVLT immediate and delayed recall (Panels A and B) and Rey CFT delayed recall (Panel C), and data of the secondary outcome measure, including gray matter volumes of the posterior cingulate cortex (PCC) and hippocampus (Panels D and E). Notes: LMM was used to test the significance of the group-by-time effects in Panel A to E (all df = 51). The paired t-test was used to test within-group differences in CAVLT immediate recall scores, Rey CFT delayed recall scores, PCC and hippocampus GMV between the baseline and post-training assessments in the training group (all df = 26). The paired t-test was used to test within-group differences in CAVLT immediate/delayed recall scores, Rey CFT delayed recall scores, and hippocampus GMV in the control group (all df = 25). The Wilcoxon test was applied to the within-group comparison of CAVLT delayed recall score in the training group and PCC GMV in the control group. ns = non-significant effects; ** p<0.001; *p<.05.



significant correlations between functional connectivity and cognitive test results were revealed.

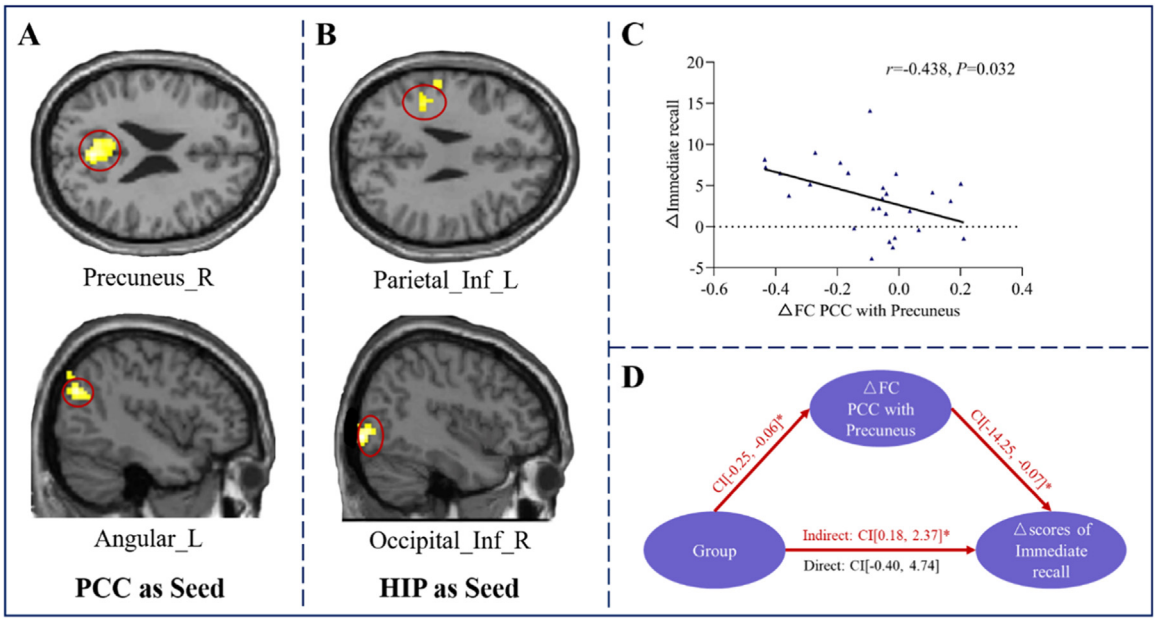
Mediating Effect of PCC_Precuneus Connectivity

The changes in the PCC_precuneus connectivity were found to be a mediating factor (bootstrapping indirect CI: [0.18, 2.37]) but not the direct effects (CI: [-0.40, 4.74]) of the CCT. In particular, the CCT had negative effects on the PCC_precuneus connectivity changes (bootstrapping CI: [-0.25, -0.06]), while the latter also had negative effects on the improvements of scores on the CAVLT immediate recall subtest (bootstrapping CI: [-14.25, -0.07]) (Fig. 2D).

Analysis of CCT Training Performance in the Training Group

To further verify the training effects, analyses were conducted on the participants' performances in the CCT training tasks between the first and last sessions. For participants who scored lower on the MoCA's Delay Recall item (n = 12, 0 to 1), the greatest training effect was in the "Working Memory" module

FIGURE 2. Functional connectivity of the posterior cingulate cortex and hippocampus (as the seeds) with neural substrates in the parietal and occipital regions, and their relationships with the participants' training-related score changes on the CAVLT immediate recall subtest. Notes: Panel A. Significant functional connectivity shown between PCC as the seed and the right precuneus and the left angular gyrus; Panel B. Significant functional connectivity shown between HIP as the seed and the left inferior parietal lobe and the right inferior occipital lobe; Panel C. Partial correlations between the changes in the functional connectivity between PCC and precuneus and change in scores on the CAVLT immediate recall subtest after controlling for age, gender, and years of education of the participants (r = -0.438, df = 22, p = 0.032); Panel D. Relationships showing how changes in the functional connectivity between PCC and precuneus mediate the training effects on improving the participants' scores on the CAVLT immediate recall subtest. PCC: Posterior Cingulate Cortex; HIP: Hippocampus; * p<0.05.



(Cohen's d = 2.573), followed by the "Attention −Divided" and "Mental Rotation" (Cohen's d = 1.960 and 1.900 respectively) (Supplementary Materials, Table 2). Improvements in the "Working Memory" module performance were significantly correlated (r = 0.593, df = 12, p = 0.042) with the participants' change scores on the CAVLT immediate recall subtest. In contrast, those who scored higher on the MoCA's Delay Recall item (n = 15, 2−4) showed a lower training effect in the "Working Memory" module (Cohen's d = 1.815) (Supplementary Materials, Table 2).

TABLE 3. Functional Connectivity of Posterior Cingulate Gyrus and Hippocampus as Seeds With Other Neural Substrates in the Parietal and Occipital Regions

				Peak MNI					
Seeds	**Contrasts**	**Brain Regions**	**Cluster**	**X**	**Y**	**Z**	**t**	P_{FDR}	**Df**
PCC	CCT>Control	No brain region above the threshold							
	CCT<Control	Precuneus_R	162	3	−66	24	−4.067	0.033	51
		Angular_L	244	−48	−75	24	−3.997	0.012	51
HIP	CCT>Control	No brain region above the threshold							
	CCT<Control	Occipital_Inf_R	371	42	−87	−6	−4.162	<0.001	51
		Parietal_Inf_L	578	−39	−30	39	−4.030	<0.001	51

Note: Voxel p<0.005 uncorrected; Cluster p<0.05 FDR corrected; PCC: posterior cingulate cortex; HIP: hippocampus; Inf: inferior; L: left, R: right.

DISCUSSION

This study explored the effects of an 8-week CCT program on improving episodic memory functions in a group of older adults with MCI. Positive training effects including improvement of participants' immediate and delayed recall functions were revealed. Our study is the first to report on the positive training effects of the Cognitive Assessment and Rehabilitation Training Machine with a randomized controlled trial combined with the brain imaging method. The MRI findings demonstrated the plasticity of the Papez circuit in response to the cognitive training. The training-related decreases in functional connectivity of the PCC and hippocampus with the occipital and parietal regions were found within the Papez circuit. However, the hypothesis that the training would increase the gray matter volumes of these two neural substrates was rejected. In particular, the decrease in connectivity between the PCC and precuneus suggests a plausible reversed age-related compensatory mechanism resulting from the cognitive training. The reversed mechanism would have facilitated the encoding and rehearsal, and hence the retrieval process in episodic memory, which was reflected by the improved post-training CAVLT immediate recall scores in the participants.

The 24-session CCT program resulted in significant improvements in the participants' verbal immediate and delayed recall, measured with CAVLT, and object delayed recall, measured with Rey CFT. Our findings were consistent with the improvements in verbal delayed recall obtained after engaging MCI participants in an 8-week CCT.[12] Li et al. [13] reported the 6-month computerized training effects covering episodic memory, working memory, visual search, and imagery, and the results showed improvements in attention, memory, and executive functions. Our results showed that the participants with more memory impairment in the training group has the greatest improvement in the "Working Memory" module, followed by the "Attention−Divided" and "Mental Rotation," while the participants with less memory impairment showed a lower training effect in the "Working Memory" module. Our findings on the participants' improved performances in the training modules concur with other studies reporting that attention and executive function (i.e., mental rotation) contribute to the encoding[43] and retrieval[44] processes in episodic memory.

The first neural effect of CTT was decreased functional connectivity between the PCC and the precuneus and angular gyrus. The decreased connectivity was associated with the participants' improvements in the immediate but not the delayed recall function. The rate limiting factor between the two types of recalls was the time available to encode and rehearse the information before memory consolidation.[45] In episodic memory, successful encoding and rehearsal can facilitate retention, and hence the retrieval. The precuneus was suggested to play important roles in the self-processing operation and mental imagery, contributing to information storage and retrieval.[46] A typical example of the processes could be to relate the cues in word-pair repetitions with one's first-person knowledge about the cue and the words. The second neural effect of CCT was decreased in the PCC_angular_gyrus connectivity. Activation of the angular gyrus in the lateral parietal cortex was associated with the retrieval process in episodic memory.[47] Angular gyrus also subserves the episodic memory buffer involving cross-modal information,[48,49] especially in its subjective recollection[49,50] and correspondence between retrieval outcomes and expectations.[51] Age-related hyper-functional connectivity among the neural substrates was found to reflect the compensatory mechanism to maintain cognitive functions among older individuals.[52] It is therefore plausible that the decrease in the PCC_precuneus and PCC_angular_gyrus connectivity is attributable to the CCT, which could have reversed the participants' compensatory mechanism. The differences in the neural processes subserved by the two PPC-related connectivity could explain why the PCC_precuneus rather than PCC_angular_gyrus connectivity modulated the participants' immediate recall changes after the CCT. In fact, the design of the "Working Memory" module in the CCT explores immediate rather than delayed recall, and no module explores the delayed recall function. Nevertheless, the CCT did not seem to significantly increase participants' volume of the PCC. Future studies should be conducted to explore the effects of adding specially designed modules for training delayed recall function and increasing the dosage of the cognitive training, and their impact on the gray matter volume of the Papez circuit neural substrates.

The CCT effects also included a decrease in the hippocampus-related connectivity. The inferior parietal

lobe plays key roles in integrating information across auditory and visual patterns,[53] and the hippocampus_inferior_parietal connectivity was reported to subserve memory formation and presentations.[54,55] Neurodegenerative changes among individuals with MCI in the inferior parietal lobe were suggested to lead to compensatory processes within the default mode network.[56] The decrease in the hippocampus_inferior_occipital connectivity suggests a positive treatment effect of cognitive training on visual processing[57] and object episodic memory.[58] In the CCT, at least four modules, namely the "Visuospatial Function," "Visual Search," "Attention," and "Working Memory," were designed to explore the visual processing functions of objects. The non-significant correlations between the hippocampus-related connectivity and the primary study outcome could be due to the mismatch in the mode of testing, that is, verbal versus object in the CAVLT, and immediate versus delayed recall in the Rey CFT.

The CCT program in this study has 11 training modules, which cover a wide variety of cognitive functions. However, there is no module that is specifically designed to train the delayed recall function. Additional modules on delayed recall function should be considered in the future development of CCT. Our findings further support the use of multidomain contents for cognitive training in individual with MCIs. The results indicate the clinical feasibility of using the Cognitive Assessment and Rehabilitation Training Machine in different hospital settings for the rehabilitation of older adults with MCI. Further studies are needed to explore whether an increase in the dosage (duration and hours) of the training would intensify the training effects. Alternative delivery modes of the training and their effects, such as hybrid (i.e., hospital-based and online) or 100% online can also be explored.

LIMITATIONS

First, the sample size of this study was relatively small, which would limit the effect sizes and generalization of the results. Although the effect sizes of most findings fall under a moderate range and the participants were typical older adults with MCI, readers should interpret the findings with caution. Future studies should consider replicating the CCT program in a larger sample size. Second, the duration and mode of contact of the health education program received by the participants in the control group could have biased the results. The fewer number of hours, that is, 8 hours (control) versus 24 hours (intervention), could have weakened the effects on the outcome measures among the control participants. In contrast, the full 1-hour face-to-face contacts for eight sessions with the clinicians in the control group, when compared with the brief contacts in each of the 24 sessions in the training group, might have constituted a placebo effect. Although the participants' performances in the CCT showed significant improvements, substantiating the training effects, future studies should replicate the study with the same exposure hours between the intervention and control groups. Third, the 8-week duration, 24-hour dosage, and without an extended follow up design could have constrained the positive effects of the cognitive training. Replication of the clinical trial with an increased dosage and a 6-month follow-up period can offer further evidence on the efficacy of the CCT. Finally, the use of resting-state MRI, which offers less precise measures of the neural processes associated with episodic memory than other methods. Event-related functional MRI with participants performing episodic memory tasks in real time can improve the specificity of the functional connectivity in future studies.

CONCLUSION

The 8-week CCT program improved the episodic memory (immediate recall) of participants with MCI. Brain imaging results indicated decreases in the functional connectivity originated from the PCC and hippocampus, as part of the Papez circuit, with neural substrates in the parietal and occipital regions. The training-related changes in the functional connectivity suggest a down-modulation of the neurodegenerative hyper-functional connectivity within the Papez circuit's neural substrates common in older adults with MCI. Our findings provide insights regarding the content design and dosage of CCT for enhancing cognitive functions of MCI individuals.

AUTHOR CONTRIBUTIONS

J.W. and Y.H. contribute to this article equally and share first authorship. L.C, C.C.H., and T.M.C.L. are co-corresponding authors. J.W.: Conceptualization, formal analysis,

methodology, and writing manuscript. Y.H.: Data collection, curation, formal analysis, methodology, and writing manuscript. S.L., Z.L., J.H.: Conceptualization, methodology, and writing manuscript. J.T., L.C., C.C.H., T.M.C.L.: Conceptualization, funding, resources, review, and editing of the manuscript. All authors read and approved the final version of this manuscript.

DISCLOSURES

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DATA STATEMENT

The dataset used is available from the corresponding author on reasonable request. The data has not been previously presented orally or by poster at scientific meetings.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.jagp.2023.04.008.

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