Received: 29 September 2021 | Revised: 18 February 2022 | Accepted: 23 February 2022

DOI: 10.1002/alz.12658

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

FEATURED ARTICLE

Tai Chi enhances cognitive training effects on delaying cognitive decline in mild cognitive impairment

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Funding information
Shanghai Municipal Science and Technology Major Project, Grant/Award Number: 2018SHZDZX05; Innovation Program of Shanghai Municipal Education Commission, Grant/Award Number: 2017-01-07-00-01-E00046; Clinical Research Center, Shanghai Jiao Tong University School of Medicine, Grant/Award Number: DLY201603; National Key R&D Program of China, Grant/Award Number: 2016YFC1305804; Shanghai Rising-Star Program, Grant/Award Number: 21QA1405800

Abstract

Introduction: Cognitive training and physical exercise have shown positive effects on delaying progression of mild cognitive impairment (MCI) to dementia.

Methods: We explored the enhancing effect from Tai Chi when it was provided with cognitive training for MCI. In the first 12 months, the cognitive training group (CT) had cognitive training, and the mixed group (MixT) had additional Tai Chi training. In the second 12 months, training was only provided for a subgroup of MixT.

Results: In the first 12 months, MixT and CT groups were benefited from training. Compared to the CT group, MixT had additional positive effects with reference to baseline. In addition, Compared to short-time training, prolonged mixed training further delayed decline in global cognition and memory. Functional magnetic resonance imaging showed more increased regional activity in both CT and MixT.

Discussion: Tai Chi enhanced cognitive training effects in MCI. Moreover, Tai Chi and cognitive mixed training showed effects on delaying cognitive decline.

KEYWORDS
cognitive training, mild cognitive impairment, mixed training, Tai Chi exercise

1 | INTRODUCTORY NARRATIVE

Mild cognitive impairment (MCI) is a clinically important stage before the onset of dementia caused by Alzheimer's disease (AD). It happens ahead of AD and ≈50% of MCI patients (roughly 12% per year) will progress to AD in the subsequent 4 to 5 years.[1] Delaying cognitive decline in MCI could contribute to fewer new AD cases, and less expenditure on care and treatment for dementia as well. As medications for AD are not generally indicated for MCI patients due to limited prevention effects as guidelines have suggested (e.g., off-label use of cholinesterase inhibitors only in the United States; no evidence in Austria and Germany),[2] non-pharmacological interventions have been largely studied for their effect on delaying cognitive deterioration. Their effects are important clinical issues remaining to be further addressed.

Currently, the main non-pharmacological interventions for MCI include cognitive training, physical exercise, diet modification, and stimulation techniques.[3–5] One early large-scale, randomized trial (the Advanced Cognitive Training for Independent and Vital Elderly study) had three models of cognitive training: speed of processing, memory, and reasoning. Each intervention modified the corresponding ability in elders, and the effect lasted for 2 years.[6] Computerized cognitive

training could be performed remotely and has been regarded as effective at protecting cognition in clinical scenarios.[7] A meta-analysis suggested computerized cognitive training has a positive effect on global cognition, selected cognitive domains, and psychosocial functioning for MCI patients.[8] The usability barrier of digital applications would be a problem if users had cognitive or perception impairment.[9] The application was designed especially for MCI and it was easily used by older adults. In our previous study, we trained MCI patients with online multi-model cognitive tasks for 6 months. MCI patients had benefits in memory, attention, and executive function. Nevertheless, in the 1-year follow-up, training effects were no longer significant.[10]

In terms of physical exercise, a Chinese traditional mind-body exercises, Tai Chi, also showed beneficial effects as an intervention for MCI. It is a mild psychophysiological exercise and is suitable and safe for elders. It consists of a combination of posture and slow movements, and participants need to memorize all postures and movements. In addition to helping with balance control, flexibility, and muscular strength,[11,12] it also emphasizes mental concentration, memorization of procedures, physical balance, and relaxation. A meta-analysis study including 12 clinical trials found that Tai Chi exercise had a large beneficial effect on global cognitive ability and long-term delayed recall ability, as well as executive function.[13]

Based on the above evidence, we first hypothesized that Tai Chi could further enhance cognitive training to help delay cognitive decline in MCI. The results would help physicians decide whether to prescribe both cognitive training and Tai Chi for MCI patients. Another key question for the clinicians is how long should the intervention last. The long-term and post-training effects of Tai Chi for MCI are unclear, and the effect of mixed cognitive and Tai Chi training also needs further assessment.

We designed the prospective clinical trial, enrolled MCI patients, and assigned them into three groups: cognitive training (CT) group, Tai Chi and cognitive training (MixT) group, and control group. To strengthen the validation and make the study more complete, we compared the group difference in cognition trend as follows. (1) We explored the immediate effect after the first 12-month training. (2) We next explored the waning effect after training in the second 12-month training (post-training effect). (3) Then, the original MixT group had training for 12 months, and a subgroup continuted training for another 12 months. We assessed the long-term effect of mixed training in a total of 24 months.

One limitation of our methods was that we only used cognitive assessments as outcomes for training effects. It may have been clinically more helpful if we could observe the difference of conversion rate to dementia between groups. Because the annual AD conversion rate of the MCI is 10% to 19% in epidemiological studies,[14,15] we would need a sample size 400 to 600 to provide enough statistical power to assess significant conversion difference between our groups. This could be achieved if there were more Tai Chi training rooms with enough capacity in further multi-center clinical trials.

In our findings, both training groups (CT and MixT) had benefit in global cognition after 12-month training, and the mixed training gained extra improvement in verbal memory, naming, and executive function.

RESEARCH IN CONTEXT

1. **Systematic review**: Currently, the main non-pharmacological interventions for mild cognitive impairment (MCI) include cognitive training, physical exercise, diet modification, and stimulation techniques. Meta-analysis suggested computerized cognitive training and Tai Chi exercise had efficacy on global cognition and selected cognitive domains for MCI patients, respectively. We hypothesized that Tai Chi could further enhance cognitive training to help delay cognitive decline in MCI. Another key question is how long the patients should take the intervention.
2. **Interpretation**: Tai Chi could additionally help verbal memory beyond cognitive training. The results also suggested that prolonged cognitive and Tai Chi training provided steady annual cognitive benefit, while the effect was generally not observed if training stopped for 12 months. This implied the necessity of continuous combined cognitive and Tai Chi physical training before the dementia stage.
3. **Future directions**: The individual variability of amyloid beta deposition in MCI could lead to sampling variability and interfere with training effects. In further studies, training effects should be assessed in larger populations with precise Alzheimer's disease–specific biomarkers to confirm whether such a non-pharmacological intervention is effective for MCI with different pathological status.

In the second 12-month = training, the MixT subclass A who stopped training had a similar trend of annual changes in cognition to the control group. In MixT subclass B, who continued training, we explored the effect of prolonged mixed training (24 months), and the results further supported the positive training effect on global cognition measured by Mini-Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog), as well as verbal memory by Auditory Verbal Learning Test (AVLT). In neuroimaging, compared to controls, training groups had increased local neural activities at bilateral precuneus, superior parietal lobules, inferior frontal gyrus,s and right middle/inferior temporal gyrus measured by functional magnetic resonance imaging (fMRI) after 12-month training.

Our results suggested effect size (ES) 1.08 by MMSE after 12-month mixed training, and ES 0.43 by 5-minute recall in AVLT of MixT over CT. The annual improvements were similar in the first and second 12 months of MixT. These results were comparable to other non-pharmacological interventions for people with cognitive impairment. The effect of multimodal cognitive enhancement therapy (cognitive training, cognitive stimulations, reality orientation, physical therapy, reminiscence therapy, and music therapy in combination) suggested improvement of MMSE (ES = 0.47) and ADAS-Cog (ES = 0.35) in MCI

and dementia (16-week intervention, n = 55) patients.[16] A 24-week aerobic and strength training suggested ES 1.6 standard deviation (SD) in MMSE for MCI patients (n = 52, with 26 per group).[17] Similar to the mixed training protocol of our study, 4-week simultaneous aerobic exercise and memory training for subjective memory impairments suggested ES 0.48 in verbal memory.[18] In a systematic review for studies of another non-pharmacological intervention, repetitive transcranial magnetic stimulation, the estimated overall ES on global cognitive performance was 0.77 (95% confidence interval: 0.57 to 0.97).[19] However, these studies were of small sample size (the largest one was 45 in total) and heterogenous intervention span (from 1 day to 6 weeks).

Based on our findings, there were two major updates from previous studies. First, most non-pharmacological interventions for MCI lasted <1 year, and their long-term effect and post-training effect were undetermined. As we have a longer intervention period, we observed that prolonged cognitive and Tai Chi training provided steady annual cognitive benefit, while the effect was generally not observed if training stopped for 12 months. Second, although long-term mixed interventions in the FINGER study showed promising results for people at risk of cognitive decline, the study only had two arms (training and control). It could not evaluate the beneficial effect from each intervention.[20] We observed the enhancing effect from Tai Chi when it was provided with cognitive training. In all, our findings suggested benefits of providing MCI patients with mixed cognitive and Tai Chi training before the dementia stage in the AD continuum.

However, as positron emission tomography (PET) for AD-specific biomarker amyloid beta (Aβ) was not performed in all MCI at baseline, the question about the interaction between AD core pathology Aβ and training effect in MCI is still unanswered. The individual variability of Aβ deposition in MCI could lead to sampling variability and interfere with training effects. In further studies, training effects should be assessed in larger populations with precise AD-specific biomarkers to confirm whether such non-pharmacological intervention is effective for patients with MCI with different pathological status.

2 | DESIGN AND CONSOLIDATED RESULTS

2.1 | Study design

The study was a prospective, randomized, single-blind clinical trial with MCI patients enrolled. The patients met the research criteria for "MCI due to AD," which was proposed by National Institute on Aging-Alzheimer's Association (NIA-AA) workgroups,[21] including both clinical features and one biomarker. The biomarker of neuronal injury for MCI was tested as the atrophy of medial temporal lobe and further defined by the visual rating medial temporal atrophy (MTA) score.

Global cognitive function was assessed at baseline and every 6 months afterward (in months 6, 12, 18, and 24) by the Chinese versions of MMSE and ADAS-Cog.[22] The specific cognitive domains (memory, executive function, attention, language, and spatial ability) were evaluated at baseline and every 12 months afterward (in month 12 and 24) by the AVLT-Huashan version,[23] the Shape Trail Test (STT, including Part A and B),[24] the Rey-Osterrieth Complex Figure Test (CFT),[24] the Stroop Color and Word Test (SCWT), and Boston Naming Test (BNT, the 30-item version). In addition to cognition evaluation, brain structure and function were assessed by MRI at baseline and in month 12.

There were two-round randomizations after inclusion. The simple randomization was performed by "randomizeR" package in R (version 3.6.2). The function (crPar and genSeq) generated a randomization sequence for grouping. The patients were randomized to the CT, MixT, or control group. After three groups were created, the 1:1 block randomization was used to assign patients in the MixT group into two classes: Class A and Class B.

For the CT group, cognitive training was carried out at patients' homes, online. The training program comprised four tasks described in the supporting information: short-term memory, speed perception, motion trace perception, and mental rotation. Patients in the CT group were asked to perform all these tasks three to four times (about 20 to 30 minutes' training) per week for 6 months, as was the MixT group.

In the MixT group, patients had Tai Chi training in addition to the above cognitive training. Tai Chi training courses were offered by a Tai Chi teacher in a gym with maximal capacity of 25 participants twice a week. Each training course lasted for 2 hours (see the Detailed Methods and Results section). After the first 12-month training, CT and MixT group Class A stopped training and were followed-up for the second 12-month period (from month 12 to month 24). Meanwhile, MixT group Class B continued cognitive and Tai Chi training (Figure 1).

For training effect, we used the Gaussian linear mixed-effects model to compare changes of cognitive scores between groups. The interaction effect between time and group represented the effect of intervention. Significance of two-sided $P < 0.05$ was used in all analyses. The standardized change scores were defined as changes between the visits divided by SD for all patients in the reference visit time. The visits included baseline, month 6, month 12 (mid-time), month 18, and month 24. The reference visit time was baseline in the first 12-month, and month 12 (mid-time) in the second 12-month follow-up. We calculated effect size for intervention by subtracting mean standardized change scores between groups that were being compared; thus, the SD was used as the unit for the longitudinal changes and group differences.

For the fMRI data analysis, we calculated the voxel-wise mean amplitude of low frequency fluctuation (ALFF) as representation of neural activity. The mixed model was also used to estimate interaction between time and group. Standardized gray matter volumes of the whole brain were used as covariates.

2.2 | Consolidated results

We first explored the immediate enhancing effect from Tai Chi after the first 12-month training. In month 12, MMSE improved 0.33 SD and 0.10 SD in the MixT and CT groups, respectively, compared to −0.75 SD in the control group (both group × time interaction effect $P < 0.001$, P-corrected by false discovery rate [FDR] < 0.001, P-corrected by Bonferroni < 0.001). The CT group showed an improvement trend in the ADAS-Cog ($P = 0.06$). In addition to positive effects in global

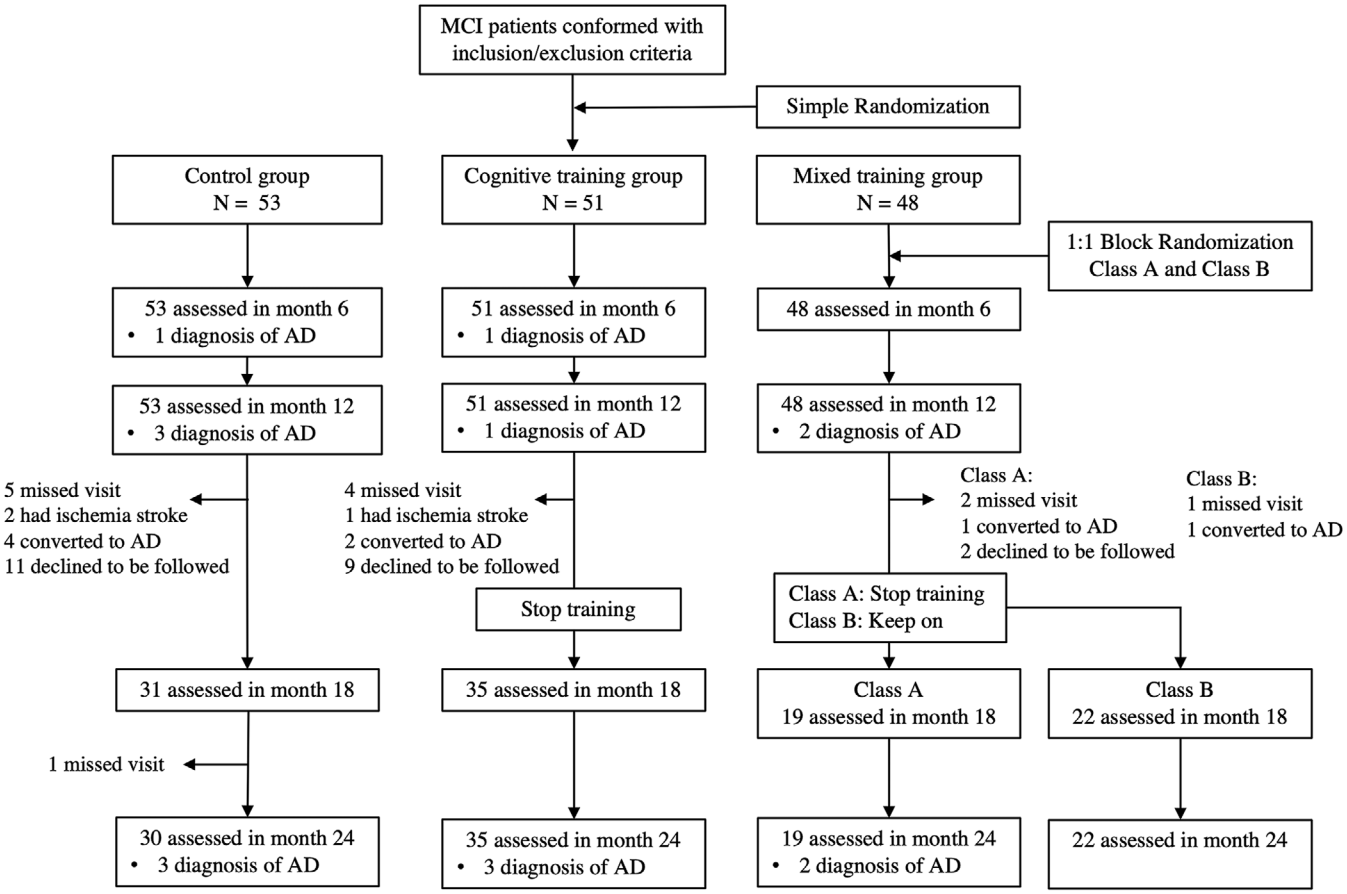

FIGURE 1 Flowchart. AD, Alzheimer's disease; MCI, mild cognitive impairment

cognition for CT and MixT over controls, effect size of verbal memory (5-minute and 20-minute recall in AVLT) were in favor of the MixT group (all *P* -corrected by FDR < 0.05, *P*-corrected by Bonferroni < 0.05). Among the two training groups, the MixT had extra benefits in AVLT 5-minute (0.43 SD, interaction *P* = 0.015, *P*-corrected by FDR = 0.037, *P*-corrected by Bonferroni = 0.134) and 20-minute (0.47 SD, interaction *P* = 0.022, *P* -corrected by FDR = 0.038, *P*-corrected by Bonferroni = 0.202) recall than CT (Figure 2, Table 1).

The individual ALFF brain maps were compared voxel-wise for the interaction effect (group × time) in mixed model analysis. Both CT and MixT had clusters of increased ALFF mainly at bilateral medial temporal lobes, temporal poles, posterior cingulate cortex, and insular cortex (Figure 3, voxel-level: *P* < 0.001, corrected cluster level: *P* < 0.001). No significantly negative difference was detected. We also used repeated measures *t*-test to further explore the source of interaction effect and observed the decreased ALFF in the above clusters in the control group. However, the CT and MixT did not have significant differences for the interaction effect in the mixed analysis model.

Then we explored the waning effect after training in the second 12-month period. In the second 12 months, all cognitive changes in MixT Class A and control were not statistically significant: The MixT Class A had changes of −0.52 SD in MMSE (vs. −1.00 SD in controls, *P* = 0.212), -0.48 SD in AVLT 5-minute recall (vs -0.49 SD in controls, *P* = 0.969), −0.67 SD in AVLT 20-minute recall (vs. −0.71 SD in controls, *P* = 0.893) and 0.97 SD in ADAS-Cog (vs. 0.89 SD in controls, *P* = 0.801). The CT showed post-training advantages over controls in MMSE (−0.12 SD vs. −1.33 SD, *P* = 0.011, *P*-corrected by FDR = 0.006, *P*-corrected by Bonferroni = 0.099), AVLT 5-minute recall (0.29 SD vs. −0.24 SD, *P* = 0.007, *P*-corrected by FDR = 0.006, *P*-corrected by Bonferroni = 0.061), AVLT 20-minute recall (0.23 SD vs. −0.24 SD, *P* < 0.001, *P*-corrected by FDR = 0.006, *P*-corrected by Bonferroni = 0.002), and ADAS-Cog (−0.09 SD vs. 0.61 SD, *P* = 0.003, *P*-corrected by FDR = 0.004, *P*-corrected by Bonferroni = 0.028).

Finally, we assessed the long-term effect of mixed training. In the second 12-month training period, 22 patients in the MixT group Class B who continued mixed training (cognitive training: 130.5 minutes/week + Tai Chi: 120 minutes/week) showed improvement over the control group of 30 patients, in MMSE (0.05 SD vs. −1.00 SD, *P* = 0.004, *P*-corrected by FDR = 0.018, *P*-corrected by Bonferroni = 0.039), AVLT 5-minute recall (0.27 SD vs. −0.49 SD, *P* = 0.034, *P*-corrected by FDR = 0.036, *P*-corrected by Bonferroni = 0.308), AVLT 20-minute recall (0.17 SD vs. −0.72 SD, *P* = 0.009, *P*-corrected by FDR = 0.019, *P*-corrected by Bonferroni = 0.081), and ADAS-Cog (0.17 SD vs. 0.89 SD, *P* = 0.034, *P*-corrected by FDR = 0.036, *P*-corrected by Bonferroni = 0.310). They also showed cognitive benefit over MixT group Class A in MMSE (*P* = 0.037, *P*-corrected by FDR = 0.044, *P*-corrected by Bonferroni = 0.334), AVLT 5-minute recall (*P* = 0.049, *P*-corrected by FDR = 0.045, *P*-corrected by Bonferroni = 0.447), AVLT

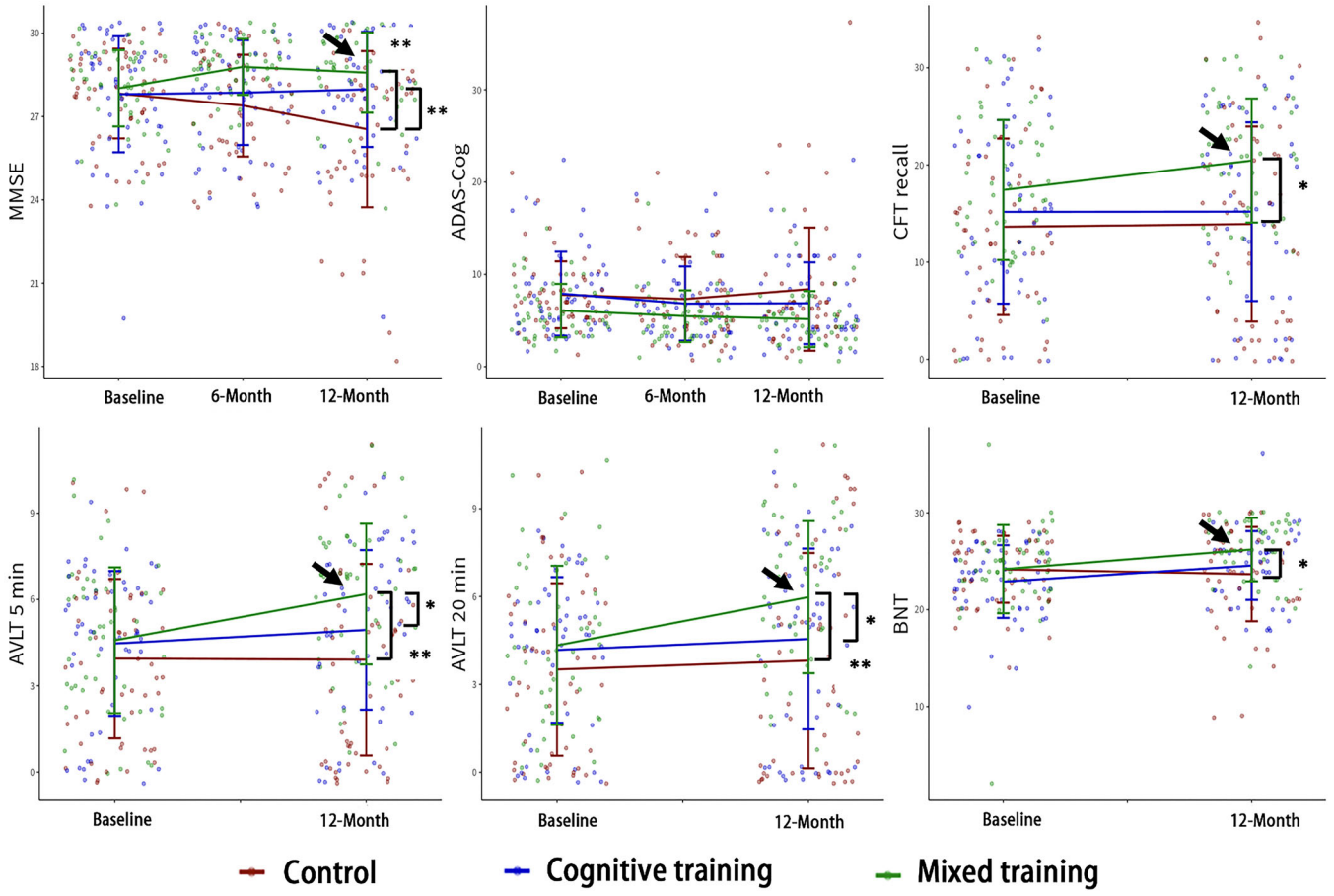

FIGURE 2 Training delayed cognitive decline during the 12-month follow-up. The mean and standard deviation were illustrated by line plot and error bars. Higher scores suggest better performance, except ADAS-Cog. The arrows indicated the differences of mixed training from the other two groups during the first 12 months. $^{*}P < 0.05$, $^{**}P < 0.01$ (two-sided) for the interaction effect of time and group by Gaussian linear mixed-effects model. ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; AVLT, Auditory Verbal Learning Test-Huashan version; BNT, Boston Naming Test; CFT, Complex Figure Test; MMSE, Mini-Mental State Examination

20-minute recall ($P = 0.035$, P-corrected by FDR = 0.044, P-corrected by Bonferroni = 0.311), and ADAS-Cog ($P = 0.031$, P-corrected by FDR = 0.043, P-corrected by Bonferroni = 0.277; Table 3, Figure 4).

3 | DETAILED METHODS

3.1 | Participants

The study was a prospective, randomized, single-blind clinical trial carried out in Rui Jin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China. Our study was approved by the Research Ethics Committee of Ruijin Hospital in November 2018. The first participant was enrolled in December 2018. Informed consent was obtained from all patients. The study was registered with ClinicalTrials.gov (NCT03119051).

We recruited MCI patients from memory clinics with cognitive complaints for at least 1 year. They were screened by the MMSE (Chinese version),[25] Zung Self-rating Anxiety Scale, and Zung Self-rating Depression scale. MCI diagnosis was made based on detailed medical history, neurological examinations, global score of Clinical Dementia Rating scale (CDR = 0.5), and MTA.[21] MTA was the biomarker for neuronal injury and defined by visual rating MTA score.[26] Because patients with MTA score ≥2.0 had greater likelihood of AD conversion, it was set as one of the inclusion criteria.[27] Exclusion criteria included other causes of dementia, as well as treatment with benzodiazepines, or antipsychotic or antiepileptic medications. Patients with poor vision or hearing were also excluded. All patients were of unrelated Chinese Han descent with >6 years of education.

Baseline demographics included sex, age, education level, occupation, body mass index (BMI), concomitant diseases, and medications. Global cognitive function was assessed at baseline and every 6 months afterward (in months 6, 12, 18, and 24) by the Chinese version of MMSE and ADAS-Cog.[22] The specific cognitive domains (memory, executive function, attention, language, and spatial ability) were evaluated at baseline and every 12 months afterward (in month 12 and 24) by the AVLT-Huashan version,[23] the STT (including Parts A and B),[24] the Rey-Osterrieth CFT,[24] the SCWT, and BNT (the 30-item version). In addition to cognition evaluation, brain structure and function were assessed by MRI at baseline and in month 12.

TABLE 1 Mean standard change in training and control groups in the first 12 months

	CT - Control[a]	MixT - Control[a]	MixT - CT[#]	CT
MMSE	0.85 (0.39 to 1.30)**	1.08 (0.63 to 1.52)**	0.22 (−0.14 to 0.58)	0.10 ± 0.96
Complex figure test				
Copy	0.23 (−0.39 to 0.85)	0.49 (−0.11 to 1.10)	0.27 (−0.17 to 0.70)	−0.23 ± 1.16
Recall	−0.03 (-0.44 to 0.38)	0.31 (0.00 to 0.63)*	0.34 (−0.05 to 0.74)	0.00 ± 1.21
AVLT				
Immediate recall	0.14 (−0.30 to 0.58)	0.60 (0.16 to 1.04)*	0.46 (−0.02 to 0.91)	0.29 ± 1.13
5-minute recall	0.19 (−0.15 to 0.54)	0.63 (0.25 to 1.01)**	0.43 (0.08 to 0.78)*	0.18 ± 0.80
20-minute recall	0.03 (−0.34 to 0.40)	0.49 (0.11 to 0.87)**	0.47 (0.07 to 0.87)*	0.14 ± 0.99
20-minute recognition	0.25 (−0.14 to 0.64)	0.30 (−0.07 to 0.44)	0.06 (−0.35 to 0.47)	0.21 ± 1.07
SWCT				
Word	−0.29 (−0.84 to 0.26)	−0.03 (−0.50 to 0.43)	0.26 (−0.17 to 0.69)	−0.11 ± 1.32
Color	−0.03 (−0.31 to 0.21)	−0.29 (−0.76 to 0.17)	−0.27 (−0.76 to 0.22)	0.03 ± 0.74
Interference	−0.24 (−0.67 to 0.19)	−0.21 (−0.55 to 0.13)	0.03 (−0.35 to 0.41)	−0.12 ± 1.18
Shape Trail Test				
STT-A	−0.31 (−0.92 to 0.30)	−0.58 (−1.12 to −0.04)*	−0.28 (−0.83 to 0.25)	0.09 ± 1.60
STT-B	−0.22 (−0.70 to 0.26)	−0.38 (−0.81 to 0.06)	−0.15 (−0.56 to 0.25)	0.07 ± 1.16
BNT	1.77 (−0.75 to 4.29)	0.63 (0.14 to 1.12)*	−1.14 (−3.66 to 1.39)	1.65 ± 8.91
ADAS-Cog	−0.43 (−0.87 to 0.02)	−0.40 (−0.87 to 0.07)	0.03 (−0.33 to 0.39)	−0.27 ± 0.83

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; AVLT, Auditory Verbal Learning Test-Huashan version; BNT, Boston Naming Test; CT, cognitive training; MixT, cognitive and Tai Chi training; MMSE, Mini-Mental State Examination; SCWT, Stroop Color-World Test; STT, Shape Trail Test.

[a]Differences were CT - Control, MixT - Control and MixT - CT.

*Uncorrected $P < 0.05$.

**Uncorrected $P < 0.01$ for the interaction effect (group × time interaction) in Gaussian linear mixed-effects model. The CT column represented mean standard changes of cognitive training group in 12 months (mean ± standard deviation).

3.2 | Study design and training protocol

After inclusion in the trial, patients were first assigned to CT, MixT, or control group by simple randomization. The simple randomization had the advantage of balancing covariates. In the MixT group, Tai Chi was trained in special gym rooms, and each room had equal capacity. In addition, each class (i.e., Class A and Class B) had an equal number of participants so they could share similar teaching time and classroom atmosphere. The 1:1 block randomization was used to assign patients in the MixT group into two classes: Class A and Class B.

Patients were not actively told the group allocation, and we also blinded neuropsychological raters and data analysts to the group allocation. Coordinators worked independently from raters, and the raters only performed neuropsychological tests for patients. Data analysts only knew the index of each group, but not group information when they did data preprocessing and group comparisons.

To minimize the Hawthorne effect,[28] all groups were informed of the study purpose at observation and follow-up, while MixT and CT groups were given additional information about training. The control group was not intervened during the follow-up, and only given general health advice. Telephone interviews were used to make sure all participants complied with our protocol. In addition, all MCI patients were not given cholinesterase inhibitors or memantine to minimize the effect of medication unless they progressed to AD in their visits during the follow-up. The AD diagnosis was confirmed by neuropsychological tests and ^{18}F florbetapir Aβ PET for Aβ.[29]

In the CT group, we modified our previous online tasks to be more concise and enjoyable.[10] There were five tasks, involving cognitive domains about memory, attention, time/speed perception, and spatial configuration. The detailed CT protocols are as follows.

For the visual working memory task, in one session, patients were asked to memorize several (two to eight cards, started from two) playing cards (targets) within some time (time [seconds] = 2 × the number of targets). Then they did a simple calculation, such as "4 + 6 = " or "5 − 3 = ." They would be presented with another group of playing cards (probes) until they calculated correctly. Then they needed to judge whether any card (target) seen before was among the probes. The number of probes is twice as many as targets. The difficulty level was self-adaptive. The number of targets doubled (two successive correct responses) or remained (one incorrect response) or decreased (two or more successive incorrect responses) in the next session.

The episodic memory task consisted of pictures (one to four pictures) depicting an event (e.g., Miss Wang is doing physical exercise in the morning in the park) presented for a few seconds. Then patients enjoyed 30-second music and scenery pictures as an interruption. After music, patients were asked questions about the event (e.g., What is

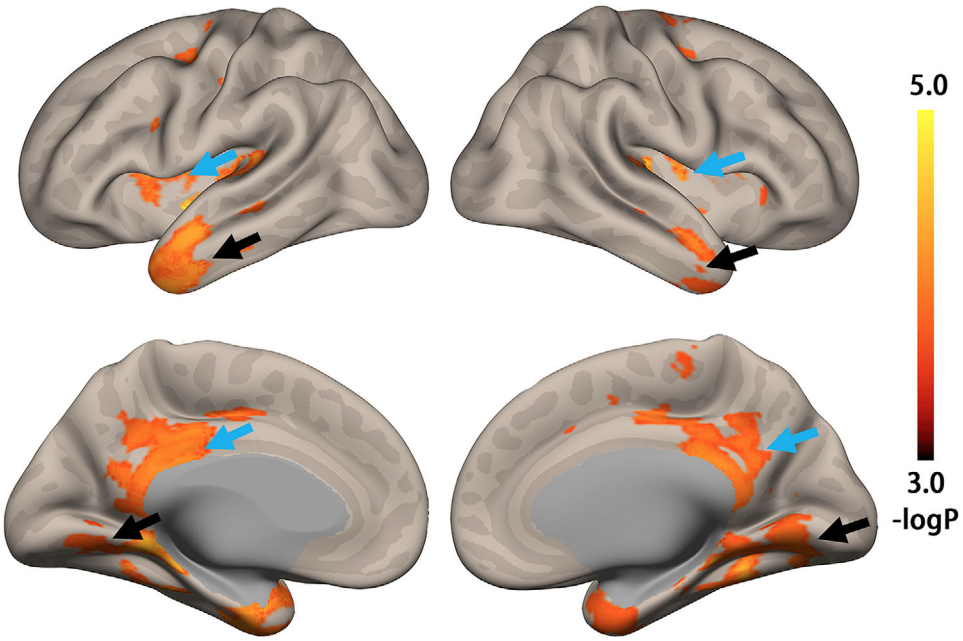

FIGURE 3 Voxel-wise results of mixed-model analyses of interaction differences (group × time interaction) in ALFF changes from baseline to 12 months. Difference = (training group at 6 months – training group at baseline) – (control group at 6 months – control group at baseline). Axial slices are shown in neurologic convention. The arrows indicated the increased ALFF of training groups in bilateral temporal lobes (black arrows in upper row), insular cortex (blue arrows in upper row), medial temporal lobes (black arrows in lower row), and posterior cingulate cortex (blue arrows in lower row). The color bar was minus base 10 logarithm of false discovery rate corrected *P*-value. ALFF, amplitude of low frequency fluctuation

Miss Wang doing in the morning at the park: doing exercise? fishing? sleeping?). Similarly, the number of pictures doubled (two successive correct responses) or remained (one incorrect response) or decreased (two or more successive incorrect responses) in the next session.

In the speed perception task, a cartoon was displayed of two cars moving toward or chasing in a street intersection. Patients were encouraged to tap a button to stop the cars immediately before they collided. The shorter the time between "stop" and "expected collision," the better was the performance. It was considered a failure when the button was tapped after collision. When difficulty level increased, there would be a cloud over the intersection as a mask. Cars disappeared in the cloud shortly after they drove into the intersection. Patients needed to estimate the collision time based on initial speed and distance of the two cars.

The motion trace perception task was a billiard game with three balls. Patients were trained to strike the cue ball (white) to hit the target ball (red) into a pocket without collision with the interference ball (black). The difficulty was the location of the black ball and whether and how it obstructed the path for the cue and target balls. Patients needed to use reflection to avoid colliding with the black ball based on their perception of motion trace.

In the mental rotation task, two "R"s (identical or mirrored "R") of different angle were presented. Patients were asked to judge whether the two letters were the same or mirrored as soon as possible.

In the MixT group, patients had Tai Chi training in addition to the above cognitive training. The standardized Sino Tai Chi was taught by professional Tai Chi coaches in classes with the following postures: *Qishi* ("starting posture"), *Shangsanbu* ("twist step"), *Yema Fenzong* ("part the wild horse's mane on both side"), *Jingang Daozhui* ("Buddha's warrior attendant pounds mortar"), *Shoushi* ("closing posture"). More detailed movements and postures are listed in the supporting information.

After the first 12-month training, CT and MixT group Class A stopped training and were followed up for the second 12-month period (from month 12 to month 24). Meanwhile, the MixT group Class B continued cognitive and Tai Chi training.

The training effect was evaluated from three aspects: (1) We compared cognitive changes in control and two training groups between baseline and month 12. We used the intention-to-treatment analysis including patients who converted to AD within the 12 months. (2) For post-training effects, we compared cognitive changes between endpoints of the first and second 12-month period in control and training groups who stopped training after the first 12 months. (3) Finally, we also evaluated cognitive change in MixT group Class B who continued training for the second 12 months, and compared it to MixT group Class A.

3.3 | MRI acquisition and processing

At baseline and end of the first 12-month period, repeated MRI was performed for neuroimaging evaluation. MRI images were acquired using a Philips Ingenia 3T MRI scanner equipped with a dStream Head-Spine coil. The patients were placed in a supine position quietly with

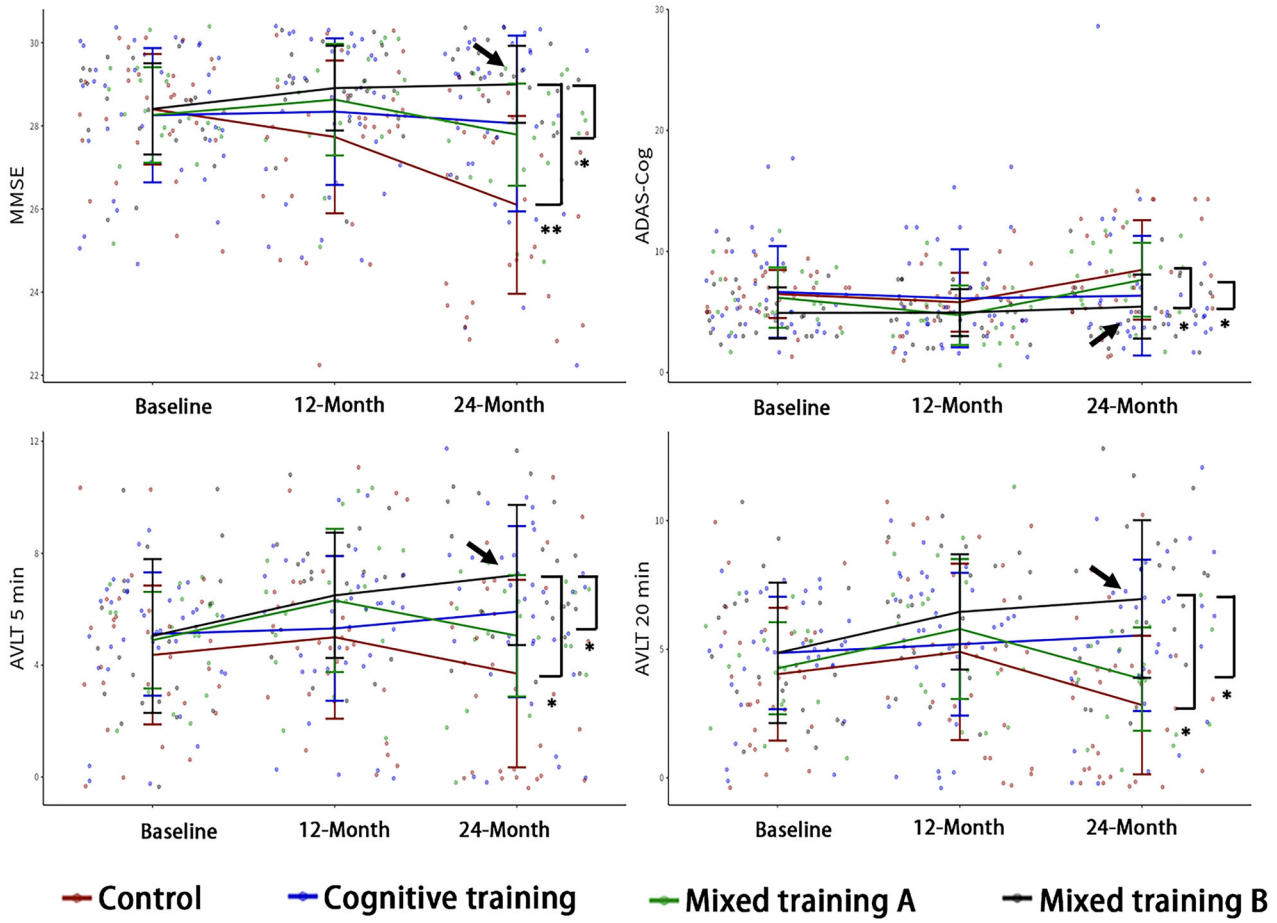

FIGURE 4 Prolonged training suggested steady effect on delaying cognitive decline in the first and second 12-month. The mean and standard deviation were illustrated by line plot and error bars. Higher scores suggest better performance, except ADAS-Cog. The arrows indicated the improvement of mixed training class B over control and mixed training class A. $^{*}P < 0.05$, $^{**}P < 0.01$ (two-sided) for the interaction effect of time and group by Gaussian linear mixed-effects model. ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; AVLT, Auditory Verbal Learning Test-Huashan version; MMSE, Mini-Mental State Examination. $^{*}p < 0.05$, $^{**}p < 0.01$

their eyes closed but asked to stay awake during the MRI. The MR sequences included high-resolution 3-dimensional T1-weighted imaging and resting-state blood-oxygen-level dependent functional MRI (BOLD-fMRI).

High-resolution T1-weighted images were acquired as the templates of further functional images for co-registration. The sequences had the following parameters: repetition time (TR) = 7.031 milliseconds, echo time (TE) = 3.189 milliseconds, field of view (FOV) = 256 × 256 mm, flip angle = 7 degrees, thickness = 1.0 mm, no interslice gap, acquisition matrix = 256 × 256, number of excitations (NEX) = 1, bandwidth = 241 Hz, and scan time = 141.919 s. All of the brain data were acquired in the sagittal plane, yielding 192 continuous slices with an acquired voxel size of $1 \times 1 \times 1\ mm^3$.

The BOLD-fMRI was carried out using gradient echo-planar imaging with the following parameters: TR = 2000 milliseconds, TE = 30 milliseconds, resolution = 3.0 × 3.0 × 3.0 mm, number of slices = 39, thickness = 3 mm, scan time = ≈7 minutes. A total of 240 echo-planar images were acquired.

We preprocessed fMRI by pipeline implemented in the CONN toolbox (version19.c; https://www.nitrc.org/projects/conn) within MATLAB. This pre-processing included removal of first five time points, slice timing correction, realignment, co-reregistration the functional scans to structural scans, then normalization to Montreal Neurological Institute space and spatial smoothing (Gaussian kernel of 8 mm full width half maximum). In the denoising step, linear regression was used to remove the influence from: (1) BOLD signal from the white matter and CSF voxels (five components each, derived using the anatomical component-based correction implemented using the ART toolbox), (2) six residual head motion parameters and their first order temporal derivatives, and (3) scrubbing of artifact/outlier scans. After linear detrending, we calculated the voxel-wise mean ALFF, which was the BOLD power within the frequency band of interest (0.01 to 0.1 Hz). Voxel-based morphometry of gray matter was also calculated as covariate volume.

3.4 | Statistical analysis

At baseline, demographics and neuropsychological scores were compared among three groups by one-way analysis of variance with

post-hoc tests or Cchi-square tests. Two classes in the MixT group (Class A and Class B) were further compared by independent *t*-tests or Chi-square tests for continuous or categorical variables in baseline and month 12, respectively. For training effect, we used the Gaussian linear mixed-effects model by "nlme" package in R (Version 3.6.2) to compare changes of cognitive scores between groups, adjusting for age and sex. The interaction effect between time and group represented the effect of intervention. Significance of two-sided $P < 0.05$ was used in all analyses. To reduce the false positives from multiple comparisons, we controlled the FDR by "fdrtool" package in R for *P*-values in each comparison for training effects between two groups in MMSE, CFT-recall, AVLT-immediate recall, AVLT 5-minute recall, AVLT 20-minute recall, SCWT-interference, STT, BNT, and ADAS-Cog. The *P*-values corrected by Bonferroni method were also reported in the significance results above.

The standardized change scores were defined as changes between the visits divided by SD for all patients in the reference visit time. For clear comparison of annual changes, we used SDs of neuropsychological tests at baseline as the units for the first 12-month changes. Due to some drop-out cases in the second 12 months, we set SDs of neuropsychological tests in patients who did not drop out as the units for the second 12-month changes. Similar to our previous study,[10] we calculated effect size for intervention by subtracting mean standardized change scores between groups that were compared.

In our variables, the MMSE and ADAS-Cog were used as the global cognitive function. The AVLT represented the immediate and delayed verbal memory (5 and 20 minutes). The STT and SCWT suggested the comprehensive ability of executive function and attention, and BNT suggested naming ability. The copy of CFT involved visuospatial domain of cognition and recall of CFT represented the visuospatial memory.

For the fMRI data analysis, the mixed model was also used to estimate interaction between time and group. Standardized gray matter volumes of the whole brain were used as covariates. Regarding to multiple comparison correction, FDR-corrected cluster-level *P*-values are computed using the standard Benjamini and Hochberg's FDR algorithm from the estimated uncorrected *P*-values.[30]

4 | DETAILED RESULTS

4.1 | Detailed demographics

A total of 152 MCI patients were enrolled in and finished the first 12-month follow-up. In the control group, 53 patients completed the assessments in month 12. Among them, four patients (7.5%) converted to AD and 31 MCI patients were continuously observed for the second 12-month period. In the CT group with 51 patients, 2 patients progressed to AD (3.9%) and 34 MCI patients were followed up for another 12 months without training. The MixT group had 48 patients and 2 were diagnosed with AD in month 12 (4.2%). The Class A in MixT group stopped, while Class B continued mixed training. A total of 19 patients in Class A and 22 patients in Class B were followed up for the second 12-month period (Figure 1).

At baseline, the three groups had similar demographic characters, including age, level of education, exercise habits, and BMI. They also matched with each other in diabetes, hypertension, smoke, statin use, and apolipoprotein E $\varepsilon 4$ status. All groups had generally similar performance in assessments of MMSE, CFT, AVLT, and SWCT color and interference score. The CT group had more female patients, and also showed slower performance in STT-A and STT-B ($P = 0.019$ and 0.039). The MixT had a very slight advantage in ADAS-Cog than the other two groups (Table 2). As MixT group had Class A and Class B, the two classes were matched in age, sex, education, comorbidities, and general cognitive performance at baseline (Table S1 in supporting information). Except for STT-B and CFT, their cognitive performance was not different from each other in month 12 (Table S2 in supporting information).

4.2 | Details in training effect

During the first 12 months, the CT and MixT group had similar cognitive training duration (131.4 minutes/week vs. 128.6 minutes/week, $P = 0.724$), while MixT had extra Tai Chi training of 120 minutes per week (60 minutes/time, twice a week). After adjusting for sex and education in the mixed model, CT and MixT groups had beneficial effects in global cognition, and the MixT group had additional improvement in delayed verbal memory as described in Section 2.2.

For detailed inspection, we found the beneficial trend of training in the first 6 months. In month 6, we observed significant beneficial effects in MMSE for MixT (effect size: 0.70 SD, interaction $P < 0.001$), and marginally significant benefit for CT (effect size: 0.28 SD, interaction $P = 0.09$) compared to controls (Figure 2). In the Figure 2 for raw score changes, the control (red line) showed decline in MMSE, CFT recall, AVLT 5-/20-minute recall, and BNT from baseline to month 12, while the MixT group (green line) had improvement in the same period. The MixT group showed enhanced beneficial effects in MMSE and AVLT 5-/20-minute recall over CT group (blue line). The arrows and asterisks indicated the significance of improvement of MixT over control and CT groups, evaluated by the Gaussian linear mixed-effects model.

Then, we validated the results in the subpopulation who were followed up in the second 12-month period. In this subpopulation (control, CT, and MixT group Class A) who did not have any training in the second 12-month period, we first re-assessed their training effect in the first 12 months. Similar to the full sample in Section 2.2, we also found MMSE improvement in the CT (35 patients) and MixT Class A (19 patients) groups in the first 12 months. The standardized change was redefined by SD of the subpopulation. MMSE improved 0.26 SD and 0.06 SD in the MixT and CT groups, respectively, compared to −0.47 SD in the control group.

The waning effect after training was evaluated afterward. During the second 12-month period, cognitive changes in MixT Class A (19 patients) and control (30 patients) groups were not statistically significant. For AD conversion, none in the MixT group Class B progressed to AD, while 3 in 30 patients (10%) of the control group, 3 in 35 (8.5%) of

TABLE 2 Baseline characteristics of groups

Baseline	Control	CT	MixT	*P*-Value
Number (*n*)	53	51	48	–
Sex (female)	29/53	40/51	34/48	0.030
Age (years)	66.6 ± 7.1	65.5 ± 7.2	65.6 ± 5.6	0.640
Years of education	12.3 ± 2.8	12.3 ± 2.6	13.4 ± 2.5	0.060
Diabetes	6/53	8/51	7/48	0.798
Hypertension	14/53	16/51	14/48	0.855
BMI (kg/m^2)	23.8 ± 3.3	23.4 ± 4.0	23.6 ± 3.4	0.858
Smoke	9/53	8/51	6/48	0.814
Hyperlipidemia	14/53	16/51	14/48	0.855
Statin use	9/53	6/51	8/48	0.712
Alcohol intake	12/53	8/51	5/48	0.280
Carotid artery disease	2/53	1/51	1/48	0.415
Atrial fibrillation	3/53	0/51	0/48	0.230
Systolic BP (mmHg)	120.2 ± 14.9	123.4 ± 15.2	122.8 ± 14.7	0.598
Diastolic BP (mmHg)	74.1 ± 9.9	76.4 ± 9.5	76.9 ± 9.5	0.380
Family history of stroke	5/53	5/51	8/48	0.548
Peripheral artery disease	1/53	0/51	0/48	0.402
Exercise (>2.5 hour/week)	15/53	14/51	12/48	0.880
*APOE ε*4 carrier	12/53	16/51	14/48	0.647
MMSE	27.8 ± 1.6	27.8 ± 2.1	28.0 ± 1.4	0.870
Complex figure test				
Copy	34.0 ± 4.7	34.0 ± 4.1	34.8 ± 4.5	0.626
Recall	13.6 ± 9.1	15.2 ± 9.4	17.4 ± 7.2	0.092
AVLT				
Immediate recall	5.0 ± 1.6	5.1 ± 1.5	5.4 ± 1.3	0.345
5-minute recall	3.9 ± 2.8	4.5 ± 2.5	4.6 ± 2.5	0.399
20-minute recall	3.5 ± 2.9	4.1 ± 2.5	4.3 ± 2.7	0.269
20-minute recognition	18.8 ± 3.6	19.9 ± 3.2	20.1 ± 3.0	0.116
SWCT (second)				
Word	28.7 ± 8.1	28.7 ± 9.9	25.1 ± 5.5	0.043
Color	39.6 ± 10.4	41.1 ± 17.7	46.3 ± 49.7	0.520
Interference	80.1 ± 20.7	89.7 ± 46.9	75.4 ± 27.6	0.128
Shape Trail Test (second)				
STT-A	62.0 ± 18.6	73.0 ± 30.4	61.2 ± 18.9	0.019
STT-B	151.3 ± 57.9	170.3 ± 73.2	138.2 ± 54.2	0.039
BNT	24.1 ± 3.4	22.9 ± 3.8	24.3 ± 4.5	0.171
ADAS-Cog	7.8 ± 3.6	7.9 ± 4.5	6.0 ± 2.9	0.028

Notes: The comorbidities of diabetes, hypertension, hyperlipidemia, statin use, carotid artery disease, atrial fibrillation, family history of stroke, and peripheral artery disease were self-reported and confirmed by medical record. Education, smoking, alcohol intake, and exercise status were self-reported. Alcohol intake was defined as "over two standard drinks per day on average."

P-Value (two-sided): one-way analysis of variance for continuous variables or Chi-square tests for categorical variables.

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; *APOE*, apolipoprotein E; AVLT, Auditory Verbal Learning Test-Huashan version; BMI, body mass index; BNT, Boston Naming Test; BP, blood pressure; CT, cognitive training; MixT, cognitive and Tai Chi training; MMSE, Mini-Mental State Examination; SCWT, Stroop Color-World Test; STT, Shape Trail Test.

TABLE 3 Mean standard change comparison in the second 12-month follow-up

	MixT Class B - Con[a]	MixT Class B - MixT Class A[a]	MixT Class A - Con[a]
MMSE	1.05 (0.40 to 1.71)**	0.57 (0.03 to 1.11)*	0.48 (−0.21 to 1.18)
Complex figure test			
Copy	0.50 (−0.16 to 1.16)	0.03 (−0.51 to 0.57)	0.47 (−0.35 to 1.30)
Recall	−0.43 (−1.16 to 0.29)	−0.43 (−1.13 to 0.26)	0.00 (−0.66 to 0.66)
AVLT			
Immediate recall	0.42 (−0.24 to 1.09)	0.48 (−0.21 to 1.16)	−0.05 (−0.76 to 0.66)
5-minute recall	0.76 (0.06 to 1.46)*	0.75 (0.01 to 1.49)*	0.01 (−0.69 to 0.72)
20-minute recall	0.89 (0.20 to 1.58)**	0.85 (0.08 to 1.62)*	0.04 (−0.58 to 0.67)
20-minute recognition	0.46 (−0.23 to 1.15)	0.58 (0.07 to 1.09)*	−0.12 (−0.81 to 0.57)
SWCT			
Word	−0.09 (−0.74 to 0.56)	−0.23 (−0.07 to 0.27)	0.14 (−0.54 to 0.83)
Color	−0.07 (−0.59 to 0.45)	−0.27 (−0.81 to 0.27)	0.20 (−0.39 to 0.0.80)
Interference	−0.35 (−0.89 to 0.20)	−0.18 (−0.68 to 0.31)	−0.16 (−0.75 to 0.43)
Shape Trail Test			
STT-A	−0.18 (−0.67 to 0.31)	−0.10 (−0.65 to 0.45)	−0.08 (−0.65 to 0.48)
STT-B	0.58 (−0.08 to 1.24)	0.42 (−0.36 to 1.19)	0.17 (−0.65 to 0.98)
BNT	0.02 (−0.08 to 0.11)	0.05 (−0.04 to 0.14)	−0.03 (−0.14 to 0.07)
ADAS-Cog	−0.72 (−1.39 to −0.05)*	−0.80 (−1.53 to −0.08)*	0.08 (−0.58 to 0.76)

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; AVLT, Auditory Verbal Learning Test-Huashan version; BNT, Boston Naming Test; CT, cognitive training; MixT Class A, cognitive and Tai Chi training group that shopped training after first 12-month period; MixT Class B, cognitive and Tai Chi training group that continued training after first 12-month period; MMSE, Mini-Mental State Examination; STT, Shape Trail Test; SCWT, Stroop Color-World Test.

[a]Differences were CT - Control, MixT - Control and MixT - CT.

*Uncorrected $P < 0.05$.

**Uncorrected $P < 0.01$ for the interaction effect (group × time interaction) in Gaussian linear mixed-effects model.

the CT group, and 2 in 19 (10.5%) of the MixT group Class A converted to AD in the period.

Finally, we observed the long-term beneficial effect on cognition by mixed training. Although the CT group had positive cognitive changes over controls after they stopped training, there was no significant difference in cognitive changes in the second 12-month period from the MixT group Class B (Figure 4). Figure 4 shows raw score changes instead of effect size. The control (red line) and MixT group Class A (green line) showed decline in MMSE, ADAS-Cog, and AVLT 5-/20-minute recall from month 12 to month 24, while MixT group Class B (black line) had improvement in the same period.

5 | DISCUSSION

In the study, we estimated the interventional effect of both cognitive training and mixed training (cognitive and Tai Chi training) in MCI patients. After a 12-month training period, both training groups had benefits in global cognition, and the mixed training group gained extra improvement in verbal memory, naming, and executive function. The enhanced effect from mixed training was further validated in the subgroups who were followed-up for an additional 12 months. After training, the MixT Class A, which stopped training, and the control group had similar trend of changes in cognition, and controls had a bit faster decrease in MMSE and AVLT recalls. In addition, we explored the effect of prolonged mixed training (24 months) and the results implied that the prolonged training could delay the cognitive decline measured by MMSE and ADAS-Cog, as well as verbal memory by AVLT.

Regarding the statistical significance defined by different *P*-values before and after multiple comparison corrections, both CT and MixT had advantages over controls even after the strictest correction by Bonferroni. However, the advantage of MixT over CT was regarded significant after FDR correction, but not Bonferroni correction as was the effect of prolonged training. The interpretation of significance involves the balance of false positives (from uncorrected *P*-value) and false negatives (from Bonferroni corrected *P*-value). Generally, the results from Bonferroni correction would be used when it was highly risky or costly to apply the results. However, our study was exploratory to accept potentially effective therapy, and cognitive and Tai Chi training were non-risky in daily life. The results after FDR correction were suggestive in the current study.

Similar to other studies for MCI interventions,[31] we first evaluated group difference in multiple cognitive domains immediately after training. As suggested by various cognitive training studies for MCI,[32] we incorporated short-term memory, attention, and spatial and temporal

perception into tasks. Although patients who converted to AD could not tolerate intensive training and reduced their involvement, we used intention-to-treat analysis to minimize attribution bias. We observed benefits in global cognition measured by the Chinese version of MMSE since month 6, and greater benefits in month 12 both by MMSE and ADAS-Cog. Regarding global cognitive function, we observed a 12-month effect size of 0.85 in MMSE in favor of the CT group, which were consistent to effect size in a multimodal cognitive enhancement therapy (effect size = 0.47 in 4 months by MMSE) for MCI.[16] Different from previous studies,[10,33] the CT group did not show great improvement over controls in memory domains. As transfer effect was usually merely in cognitive training,[34] the reason for less benefit for CT was probably due to lack of long-term memory tasks (>5 minutes) in our current task battery.

In addition to cognitive training, patients in the MixT groups had Tai Chi training physically together, and they could have mutual psychological support as in group therapy. In all, Tai Chi has a great potential as a rehabilitation intervention for mental and psychological conditions.[35] Meta-analyses suggested that Tai Chi could have potentially beneficial effects on the older adults such as preserving or improving global cognitive function, memory and learning, mental speed and attention, and also lowering the risk of dementia.[36,37] In one study for subjective memory impairments, patients who completed 4-week simultaneous performance of memory training and aerobic exercise, in simultaneous training group had a significant improvement on composite memory over a sequentially training group. The effect size (0.42) of simultaneous training on memory was also similar to that of our mixed training (0.43 to 0.47 over the CT group).

The resting-state fMRI provided brain activity changes between training groups and controls. The ALFF in controls, as the representation of intensity of regional spontaneous brain activity, decreased mainly in the bilateral posterior cingulate cortex, medial temporal lobes, temporal poles, and insular cortex. The posterior cingulate cortex is the hub of the default mode network, and decreased ALFF in bilateral precuneus is suggested as the classification of AD from controls.[38,39] It suggested that the controls developed more AD characteristics than training participants. In addition, cognitive intervention enhanced neural activities in both healthy young and elder adults. It was suggested that elder adults showed increased ALFF in the middle/superior frontal gyrus and anterior cerebellum lobe after given memory and social support.[40] Similarly, 3-month aerobic dance for MCI caused increased ALFF in the bilateral entorhinal, anterior cingulate, and para-hippocampal/medial temporal cortex while controls had decreased ALFF in the posterior cingulate cortex.[41] Although we did not observe significant enhanced effect by ALFF in repeated measures for training participants, mixed models suggested reduced decline in neural activity after training compared to controls.

It is still unclear how long the interventional effect lasts for MCI. As there were few studies designed for post-training effects on MCI that had great clinical implications, we extended our evaluation of the effect with a longer training period compared to our previous study.[10] We observed similar decline in control group and the mixed training group that stopped training for 12 months. The disappearance of interventional effect within 12 months was in line with training studies for elders.[42,43]

It is notable that the CT subgroup and MixT Class B had similar advantages over MixT Class A/control even after training in CT. As MixT Class A and CT both had identical cognitive training of similar duration, the difference in post-training effects might be attributed to random error in the small sample size of CT subgroup ($n = 35$), or MCI sampling variability. More AD key biomarker assessments in the baseline would help to reduce heterogeneity in MCI inclusion in further work.

Finally, the MixT Class B had prolonged mixed training (24 months) and they improved in global cognition by MMSE and ADAS-Cog, as well as verbal memory by AVLT. The results consolidated the beneficial effect of mixed training. We observed similar annual effect size differences in MixT group compared to control group: 1.01 SD in the first 12 months and 1.05 SD in the second 12 months by MMSE, and 0.63 SD and 0.76 SD by AVLT 5-minute recall. It suggested steady beneficial effect trends in cognition performance related to our training program.

Regarding the conversion of MCI to AD, we observed that the control group had decline in MMSE for about two points per 12-month period. It is noted that the Chinese-version MMSE has been validated in China for >20 years and its norm and longitudinal changes in MCI patients have been greatly studied. It decreased by 0.6 to 2 per year in MCI patients.[44,45] In MCI who were progressing to AD, the annual decrease of MMSE mainly distributed between two to four points.[46] It suggested that our controls had high risk of conversion to AD, and the advantage in cognitive changes of two training groups indicated lower risk in annual AD conversion.

5.1 | Limitations

Our study was different from clinical trials for drugs that had placebos and patients who were blind to their treatment. As the MCI patients were not given medications for dementia, patients in the control group were more likely to drop out in the beginning of the second 12-month period as they wanted to receive medications. The CT group also had some missing cases in the second 12-month period as the online training was boring for some individuals. The MixT group had person-to-person interactions and patients were of higher compliance. There were fewer drop-out cases in the MixT group, especially in Class B.

Our study has some other limitations. First, we observed cognitive benefits in the MixT group. However, we did not find the difference of conversion rate to dementia between groups due to the limited sample size. Because dementia poses much threat to daily life activities, it would be clinically more helpful if the interventional effect on annual AD conversion rate could be found. In the present study, the annual AD conversion rate of the control group was 7.5% (4 in 53) in the first 12 months. The CT and MixT groups had a bit lower rate: 3.9% (2 in 51) and 4.2% (2 in 48). Although the AD conversion rate was highest in the control group, the sample size could not provide enough statistical power for significant difference between the groups. We would need sample size of 200 per group to provide enough statistical power.

However, both CT and MixT had conversion rate much lower than that in other epidemiological studies (10% to 19%) for MCI.[14,15] Second, the AD diagnosis was confirmed by PET for AD-specific biomarker Aβ, while it was not performed in all MCI patients at baseline. When we started to enroll MCI patients in 2017, the Aβ biomarker was optional for MCI diagnosis as suggested by NIA-AA 2011 biomarker criteria.

5.2 | Implication and future directions

This study was the first time that 2-year cognitive and Tai Chi mixed training was evaluated in MCI. As it was unclear whether long-term training had steady beneficial effect in the course of MCI, we provided new evidence that insistence on mixed training delayed the cognitive decline for at least 2 years. Mixed training was suggested to promote the interventional effect. We also observed waning effect after training. The current treatment for MCI has various options, including medications, diet, lifestyle, cognitive training, physical therapy, etc. The above results implied the prescription of both cognitive and mild physical (i.e., Tai Chi) training for MCI patients.

In the current study, we performed and suggested the positive results from the cognitive training of about 120 minutes/week and Tai Chi training of 120 minutes/week. The current time of training provided preliminary evidence for prescription. The optimal time of training will be studied and determined further as it is critical for clinical practice. In addition, training effect should be assessed in larger populations with precise AD-specific biomarkers to check whether such non-pharmacological intervention is effective for MCI patientswith different pathological status.

ACKNOWLEDGMENTS

We thank all the patients who participated in this study. We also thank all the coaches of Sino Taiji of Fuxing International for their Tai Chi training courses to the patients. The trial is supported by the Shanghai Municipal Science and Technology Major Project Grant (2018SHZDZX05), Innovation Program of Shanghai Municipal Education Commission (2017-01-07-00-01-E00046), Clinical Research Center, Shanghai Jiao Tong University School of Medicine (DLY201603), National Key R&D Program of China (2016YFC1305804), and Shanghai Rising-Star Program (21QA1405800).

CONFLICTS OF INTEREST

All authors have no relationships/activities/interests to disclose related to the content of this submission.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Li B, Tang H, He G, et al. Tai Chi enhances cognitive training effects on delaying cognitive decline in mild cognitive impairment. *Alzheimer's Dement*. 2023;19:136–149. https://doi.org/10.1002/alz.12658