

Improved Mood Boosts Memory Training Gains in Older Adults With Subjective Memory Complaints: A Randomized Controlled Trial

Shufei Yin

Hubei University

Xinyi Zhu

Institute of Psychology Chinese Academy of Sciences

Rui Li

Institute of Psychology Chinese Academy of Sciences

Lijuan Huo

Institute of Psychology Chinese Academy of Sciences

Weicong Ren

Institute of Psychology Chinese Academy of Sciences

Qiaoling Xiao

Institute of Psychology Chinese Academy of Sciences

Minjia Lang

Institute of Psychology Chinese Academy of Sciences

Jin Li

Institute of Psychology Chinese Academy of Sciences

Jianhua Hou

Institute of Psychology Chinese Academy of Sciences

Yanan Niu

Institute of Psychology Chinese Academy of Sciences

Juan Li (✉ lijuan@psych.ac.cn)

Institute of Psychology Chinese Academy of Sciences <https://orcid.org/0000-0003-2780-9523>

Research

Keywords: subjective memory complaints, memory training, depression and anxiety, hippocampus

Posted Date: February 2nd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-164434/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Objective: Older adults with subjective memory complaints (SMC) have a higher risk of dementia and commonly demonstrate symptoms of depression and anxiety. The study aimed to examine the effect of a memory training program for individuals with SMC, and whether memory training combined with group counseling aimed at alleviating depression and anxiety would boost memory training gains.

Design: A three-armed, double-blind, randomized controlled trial.

Setting and Participants: Community-dwelling older adults with SMC, aged ≥ 60 years.

Methods: Participants ($n = 124$) were randomly assigned to memory training (MT), group counseling (GC), or GC+MT intervention. The GC+MT group received 4-hour group counseling followed by a 4-week memory training, while the MT group attended reading and memory training, and the GC group received group counseling and health lectures. Cognitive function and symptoms of depression and anxiety were assessed at baseline, mid-, and post-intervention. The GC+MT group and GC group had resting-state functional magnetic resonance imaging at mid- and post-intervention.

Results: After group counseling, the GC+MT and GC groups showed reduced symptoms of anxiety and depression, compared to the MT group. Memory training enhanced memory performance in both MT and GC+MT groups, but the GC+MT group demonstrated larger memory improvement (Cohen's $d = 0.96$) than the MT group (Cohen's $d = 0.62$). Amygdala-hippocampus connectivity was associated with improved mood and memory gains.

Conclusion and Implications: Group counseling reduced symptoms of anxiety and depression, and memory training enhanced memory performance. Specifically, improved mood induced larger memory training effects. The results suggest that it may need to include treatment for depression and anxiety in memory intervention for older adults with SMC.

Trial Registration: ChiCTR-IOR-15006165 in the Chinese Clinical Trial Registry.

Introduction

Individuals with subjective memory complaints (SMC) report declining memory without measurable cognitive deficits. SMC crosses the boundary between normal aging and mild cognitive impairment [1, 2], and is associated with higher risks of subsequent cognitive decline and dementia [3, 4], as well as poor quality of life [5]. Cross-sectional and longitudinal evidence shows individuals with SMC have increased likelihood to manifest Alzheimer's Disease biomarkers such as brain amyloid deposition [6, 7], glucose hypometabolism [7], and hippocampal volume loss [8]. SMC is considered as a "promising" stage for non-pharmacologic interventions aimed at delaying cognitive decline and preventing cognitive impairment [9].

Cognitive training is one of the most commonly used non-pharmacologic interventions. Some studies have shown older adults with SMC benefit from cognitive training [10–12], while others failed to find significant cognitive improvement training [13, 14]. A meta-analytic study [15] revealed that cognitive training could improve cognitive function in older adults with SMC, resulting in a small to moderate effect size (Hedge's $g = 0.38$). Several studies have reported structural plasticity in response to cognitive training in individuals with SMC [16, 17]. Engvig et al. (2014) found that after training, SMC participants showed an increase in gray matter volume in the brain area surrounding the episodic memory network, with the cortical volume expansion comparable to that of healthy controls [16]. In addition, individual differences in left hippocampal volume change in the SMC group were related to verbal recall improvement following training [17]. These results suggest that training-related brain changes can be evident in older adults with SMC, the earliest stage of cognitive impairment.

Individuals with SMC commonly demonstrate symptoms of depression and anxiety [18, 19]. Depression and anxiety are found detrimental to memory performance [20–22], and can lead to greater cognitive decline [23, 24], and an increased risk of progression to dementia [25, 26]. Animal studies demonstrate that exposure to psychological distress may harm older adults' memory by causing neurological deterioration to the limbic system including hippocampus [27]. As the close relationship between depression/anxiety and memory functioning, alleviating depressive and anxious symptoms may need to be

incorporated into memory training program to optimize the training efficacy [28]. There may be greater memory improvement if treatment for depression and anxiety is added to memory training in older adults with memory complaints.

To our knowledge, no experimental study has directly examined whether memory training combined with psychological interventions for depression and anxiety would outperform traditional memory training. A few training studies [29, 30] integrated stress management techniques into memory training in healthy older adults and found these comprehensive memory training programs reduced symptoms of anxiety and improved cognitive performance compared to placebo or waitlist groups. However, comparison with passive control groups cannot isolate the effect of stress management from pure memory training.

The aim of this study was to determine whether interventions for depression and anxiety would facilitate training gains on memory performance in older adults with SMC. We developed a comprehensive memory training program by combining psychological interventions with memory training. We evaluated the efficacy of combined interventions by comparing it with memory training and psychological intervention alone. We also used the resting-state functional magnetic resonance imaging (fMRI) to explore the neural mechanism of the boost effect of counseling-induced positive emotion on memory training gains. We expect that (1) the combined interventions would induce larger memory improvements than memory training or psychological intervention alone, and (2) the boost effect of improved emotion on memory training gains would be associated with the functional connectivity (FC) between hippocampus and amygdala.

Materials And Methods

Research Design

This study was an active controlled, randomized trial conducted between November 2013 and July 2014. It was registered in the Chinese Clinical Trial Registry (www.chictr.org.cn, identifier ChiCTR-IOR-15006165). The protocol was approved by the Ethics Committee of the Institute of Psychology, Chinese Academy of Sciences (CAS). All participants provided written informed consent according to institutional guidelines. The study was reported according to the Consolidated Standards of Reporting Trials [31] (CONSORT) and the extension for social and psychological interventions [32] (CONSORT-SPI; see Supplementary Materials for the CONSORT-SPI 2018 checklist).

Participants

Community-dwelling older adults were recruited from neighborhoods near the Institute of Psychology, CAS through advertisements and flyers posted in the community service stations. The inclusion criteria were: (1) age \geq 60 years; (2) education \geq 6 years; (3) a score \geq 21 on the Montreal Cognitive Assessment - Beijing Version[33] (MoCA-BJ); (4) with SMC; (5) right-handed; (6) free of neurological deficits or traumatic brain injury; (7) a score \leq 15 on the Activities of Daily Living scale[34]; (8) no severe visual or auditory impairment which would hinder intervention.

The following criteria[2] were used for screening SMC: (1) subjectively reported a decline in memory, rather than other domains of cognitive function; (2) onset of SMC within the last 5 years; (3) worries associated with memory decline; (4) feeling of worse memory performance than others of the same age group; (5) performance on the objective memory scale was within the normal range or within 1 standard deviation below the normal value. Subjective memory complaints were assessed by the Memory Inventory for the Chinese [35].

Power analysis was calculated using G*Power 3.1 [36] based on the efficacy of memory training on associative learning. A minimum sample size of $N = 93$ is necessary to detect a small to moderate effect on the within-between interaction using the repeated measures two-way analyses of variance (ANOVA) ($\alpha = 0.05$, power = 0.80, $f = 0.15$, number of groups = 3). Two hundred and nineteen participants were contacted and assessed for eligibility. One hundred and twenty-four eligible participants consented to participate in the intervention. After baseline evaluation, they were randomly allocated to three groups: memory training (MT) group ($n = 38$), group counseling (GC) group ($n = 44$), and GC + MT group ($n = 42$). A researcher who did not involve in study design, participant enrollment, intervention implementation, and assessment used SPSS 21.0 (IBM

Corporation, Somers, NY) to generate the random allocation sequence and assigned participants to three groups. Figure 1 shows the flow of the participants. Nine participants in each group discontinued intervention because of illness, time conflict, or traveling. The attrition rate was comparable among three groups. In total, 97 participants who completed intervention were analyzed.

Procedure

Three groups of participants attended seven weeks of intervention, respectively. During the first three weeks, the GC and GC + MT groups attended weekly group counseling while participants in the MT group completed reading assignments at home as control activities. From Week 4 to Week 7, the MT and GC + MT groups received memory training, and the GC group attended lectures as control activities. Group counseling, memory training and lectures were group-based, delivered at the Institute of Psychology CAS. Table 1 demonstrated details of the intervention program. Intervention and control activities were matched in frequency, duration, and format for group counseling and memory training. Participants had a break of about four weeks for Chinese New Year between Week 3 and Week 4. Cognitive assessments were administered at baseline, mid- (before Week 4), and post-intervention. The GC + MT group and GC groups had resting-state fMRI scanning at mid- and post-intervention. The pre- and post-scanning procedures were administered within a week after the completion of cognitive assessments. Participants were blind to study design and hypotheses. Counseling psychologists and training instructors were blind to study design and hypotheses, and all assessors were blind to group allocation and study design. Participants who completed intervention received a cash incentive of 300 RMB after post-intervention assessment, and those who attended fMRI scanning received extra 200 RMB.

Table 1
Intervention details for each group

| Intervention | Frequency and Duration | Description |
|---|--|--|
| Week 1–3 | | |
| Group Counseling | About 6 hours for group activities and homework. Group activities: 3 weekly sessions, 90 minutes/session | The GC and GC + MT groups attended group counseling. Group counseling was led by two licensed counseling psychologist and administrated in small groups (6–10 people). Activities were designed to provide information on aging process and cognitive aging, strategies of coping with stress and depression in late life, knowledge on lifestyle and brain health. Participants were encouraged to share personal experiences and make interpersonal communications. Homework were assigned after each session. |
| Reading (Control Activity) | Estimated 6 hours. | The MT group received reading assignments. Participants were instructed to complete reading independently at home and to record their reading progress on a log sheet. The reading materials were articles on healthy/positive aging, and strategies for coping with late-life stress and depression. |
| Week 4–7 | | |
| Memory Training | Group-based, 12 sessions in total; 3 sessions/week, 90 minutes/session | The MT and GC + MT groups attended memory training. Each session included 60-minute mnemonic training and 30-minute brain game playing. Mnemonic training was designed to promote elaborate encoding and retrieval in older adults by teaching them a series of mnemonics, including generation of mental images, item association (interactive imagery and sentence generation), and the method of loci. Participants were assigned homework to continue practicing mnemonics at home. Brain games were designed to train three components of executive function (inhibition, switching, and updating) through three tablet video games (Li et al., 2014). Training was guided by trained instructors according to a detailed manual. |
| Lectures (Control Activity) | Group-based, 12 sessions in total; 3 sessions/week, 90 minutes/session | Each session included 60-minute lecture and 30-minute casual video game playing. Lectures were about health knowledge for older adults, given by trained instructors according to a syllabus. Casual video games were commercial tile-matching games on tablets. Lectures was given by trained instructors according to a detailed manual. |
| Notes: GC, group counseling; MT, memory training. | | |

Neurocognitive Measures

A battery of tests was used to evaluate training effects on cognitive function. (1) The MoCA-BJ was used to measure global cognition. (2) Episodic memory was assessed using the Associative Learning Test [37] (ALT) and Auditory Verbal Learning Test (AVLT) WHO/UCLA version [38]. A list of 12 pairs of nouns was presented aurally to participants. Half of the word pairs were semantically associated (e.g., sun-moon; ALT-easy condition), and the other six were unrelated pairs (e.g., teacher-railway; ALT-difficult condition). Immediately After listening to the list, the first noun in each word pair was given as a cue, and participants were asked to recall the second noun. Participants scored 0.5 points for each correct answer in the easy condition (ALTeasy) and 1 point for each correct answer in the difficult condition (ALTdiff). A composite ALT score that ranged from 0 to 9 was calculated. (3) Working memory ability was measured by the Digit Span Forward (DSF) and Digit Span Backward (DSB) tasks [39].

A battery of questionnaires was used to evaluate the effects of group counseling on emotion. (1) The Self-rating Anxiety Scale [40] (SAS) was used to assess the state of anxiety. (2) Depressive symptoms were assessed using the Center of Epidemiological Survey-Depression [41] (CESD) scale. (3) Subjective well-being was measured by the Satisfaction with Life Scale [42] (SWLS). (4) Attitudes towards aging (ATA) was assessed by the Attitude Toward Own Aging Sub-Scale from the Philadelphia Geriatric Center Morale Scale [43].

Statistical Analysis of Neuropsychological Data

Baseline characteristics of the three groups (MT vs. GC + MT vs. GC) were analyzed using Pearson's *r*, chi-square, *t*, or Mann-Whitney (nonparametric) tests. Repeated measures two-way ANOVA were conducted to examine intervention effects of counseling and memory training, with Group (MT vs. GC + MT vs. GC) as the between-subject factor and Intervention (pre- vs. mid- vs. post-intervention, within-subjects) as the within-subject factor. All statistical analyses were conducted using SPSS 21.0.

Image Data Acquisition and Processing

A 3-Tesla Siemens Trio scanner (Erlangen, Germany) equipped with echo planar imaging (EPI) at the Beijing MRI Center for Brain Research was used for image acquisition. For each participant, 200 functional images were obtained using the following parameters: time repetition (TR) = 2000 ms, time echo (TE) = 30 ms, flip angle = 90°, field of view (FOV) = 200 × 200 mm², 33 axial slices, thickness = 3.0 mm, gap = 0.6 mm, acquisition matrix = 64 × 64, and in-plane resolution = 3.125 × 3.125. Resting-state fMRI data analyses were processed using the Statistical Parametric Mapping (SPM12, <http://www.fil.ion.ucl.ac.uk/spm>) and Data Processing Assistant for Resting-State fMRI (DPARSF) V2.0 (<http://www.restfmri.net>), aimed to explore the neural mechanism for the boost effect of positive mood on memory training gains. The details of image data processing have been described in the supplemental materials.

Results

Table 2 shows the demographic and clinical characteristics of the participants. Three groups did not differ significantly in gender, age, years of education, cognitive function, or emotional indicators. The adherence rate of three groups were 81.35%. No adverse events were reported by participants.

Table 2
Demographics and neuropsychological characteristics of the participants at baseline

| Characteristics | MT | GC+ MT | GC | <i>p</i> | |
|---|-------------------------|--------------|--------------|--------------|------|
| Age, years | 71.41 ± 6.56 | 74.33 ± 4.40 | 72.29 ± 6.57 | .138 | |
| Female/Male | 21/8 | 18/15 | 18/17 | .202 | |
| Education, years | 14.34 ± 2.98 | 15.39 ± 2.52 | 14.17 ± 2.82 | .158 | |
| Emotional indicators | Anxiety | 30.59 ± 5.82 | 28.94 ± 5.08 | 29.24 ± 7.62 | .524 |
| | Depression | 6.21 ± 5.56 | 5.58 ± 4.98 | 6.56 ± 6.96 | .790 |
| | Subjective well-being | 26.86 ± 4.14 | 25.88 ± 4.58 | 26.00 ± 5.83 | .701 |
| | Attitudes towards aging | 17.28 ± 3.23 | 17.24 ± 3.69 | 16.56 ± 4.32 | .690 |
| Cognitive functions | MoCA | 25.83 ± 2.22 | 26.03 ± 2.04 | 26.14 ± 2.60 | .795 |
| | Memory complaints | 3.41 ± 1.12 | 3.21 ± 0.96 | 3.14 ± 1.09 | .290 |
| | Digit span forward | 7.21 ± 1.05 | 7.36 ± 1.45 | 7.26 ± 1.25 | .882 |
| | Digit span backward | 4.83 ± 1.44 | 4.61 ± .90 | 4.83 ± 1.40 | .717 |
| | AVLT immediate recall | 6.45 ± 2.06 | 6.15 ± 2.68 | 5.77 ± 1.90 | .482 |
| | AVLT delayed recall | 11.83 ± 3.31 | 12.12 ± 3.41 | 12.06 ± 2.17 | .922 |
| | ALT | 10.31 ± 3.76 | 11.05 ± 4.16 | 9.21 ± 3.90 | .162 |
| | ALTDiff | 4.17 ± 2.93 | 4.70 ± 3.15 | 3.34 ± 2.93 | .178 |
| | ALTeasy | 6.14 ± 1.59 | 6.35 ± 1.54 | 5.90 ± 1.43 | .478 |
| Notes: MT - Memory Training, GC - Group Counseling, MoCA - the Montreal Cognitive Assessment, ALT – Associative Learning Test, ALTDiff - ALT difficult condition, ALTeasy – ALT easy condition. | | | | | |

Behavioral data on the effects of memory training and the boost effect of counseling-induced positive emotion

Effects of group counseling on emotions

ANOVA revealed significant Group × Intervention interactions in anxiety, depression, and subjective well-being, and a marginally significant interaction in ATA (Fig. 2, Table 3). Further analysis revealed that after group counseling (mid- minus pre-intervention), for the MT group, there was no significant difference in anxiety and ATA, a decrease in well-being, and an upward trend in depression, while for the GC and GC + MT groups, there was a downward trend in anxiety, no significant difference in well-being and depression, and an increase in the ATA. Results suggested that, compared with the MT group, group counseling reduced negative emotions and maintained subjective well-being.

Table 3
Emotional indicators and cognitive performance in SMC prior to and after intervention

| | MT | | | GC + MT | | | GC | | | <i>F</i> | <i>p</i> | <i>Partial η²</i> |
|--------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|----------|----------|------------------------------|
| | Pre- | Mid- | Post- | Pre- | Mid- | Post- | Pre- | Mid- | Post- | | | |
| Anxiety | 30.59 ± 5.82 | 31.59 ± 7.26 | 30.17 ± 6.42 | 28.94 ± 5.08 | 27.03 ± 5.04 | 24.63 ± 3.41 | 29.24 ± 7.62 | 26.36 ± 4.34 | 25.39 ± 4.57 | 2.82 | 0.027 | 0.058 |
| Depression | 6.21 ± 5.56 | 9.03 ± 5.56 | 7.69 ± 6.39 | 5.58 ± 4.98 | 5.55 ± 4.98 | 5.58 ± 5.97 | 6.56 ± 6.96 | 5.29 ± 6.96 | 4.15 ± 5.05 | 2.51 | 0.043 | 0.051 |
| Subjective well-being | 26.86 ± 4.14 | 25.24 ± 4.14 | 26.62 ± 5.16 | 25.88 ± 4.58 | 26.46 ± 4.58 | 28.85 ± 3.01 | 26.00 ± 5.83 | 27.53 ± 5.83 | 27.35 ± 5.15 | 3.42 | 0.010 | 0.069 |
| Attitudes towards aging | 17.28 ± 3.23 | 17.35 ± 3.23 | 17.59 ± 3.90 | 17.24 ± 3.69 | 18.94 ± 3.69 | 18.52 ± 3.42 | 16.56 ± 4.32 | 18.50 ± 4.32 | 19.29 ± 2.88 | 2.29 | 0.061 | 0.047 |
| MoCA | 25.83 ± 2.22 | 26.00 ± 1.88 | 26.41 ± 1.90 | 26.03 ± 2.04 | 26.27 ± 2.13 | 27.00 ± 1.77 | 26.14 ± 2.60 | 26.83 ± 1.97 | 26.86 ± 2.26 | 0.73 | 0.545 | 0.015 |
| Memory complaints | 3.41 ± 1.12 | 3.10 ± 1.11 | 2.69 ± 1.49 | 3.21 ± 0.96 | 3.24 ± 0.97 | 2.79 ± 1.36 | 3.14 ± 1.09 | 3.06 ± 1.03 | 2.57 ± 1.40 | 0.49 | 0.740 | 0.010 |
| Digit span forward | 7.21 ± 1.05 | 6.93 ± 1.41 | 7.45 ± 1.59 | 7.36 ± 1.45 | 7.27 ± 1.23 | 8.03 ± 1.24 | 7.26 ± 1.25 | 7.43 ± 0.98 | 7.49 ± 1.12 | 1.73 | 0.145 | 0.035 |
| Digit span backward | 4.83 ± 1.44 | 4.76 ± 1.27 | 5.52 ± 1.33 | 4.61 ± .90 | 4.76 ± 1.39 | 5.21 ± 1.39 | 4.83 ± 1.40 | 4.80 ± 1.64 | 4.94 ± 1.37 | 1.18 | 0.320 | 0.025 |
| AVLT immediate recall | 6.45 ± 2.06 | 6.62 ± 2.37 | 8.38 ± 2.29 | 6.15 ± 2.68 | 6.88 ± 2.41 | 8.03 ± 3.18 | 5.77 ± 1.90 | 6.91 ± 1.50 | 7.00 ± 1.33 | 2.14 | 0.077 | 0.044 |
| AVLT delayed recall | 11.83 ± 3.31 | 12.07 ± 1.69 | 13.24 ± 1.79 | 12.12 ± 3.41 | 12.12 ± 2.03 | 13.21 ± 1.47 | 12.06 ± 2.17 | 12.40 ± 2.67 | 12.89 ± 2.73 | 0.42 | 0.798 | 0.009 |
| ALT | 10.31 ± 3.76 | 12.69 ± 3.76 | 15.98 ± 3.51 | 11.05 ± 4.16 | 13.32 ± 4.16 | 17.18 ± 4.15 | 9.21 ± 3.90 | 12.29 ± 3.90 | 13.47 ± 4.47 | 3.16 | 0.015 | 0.063 |
| ALTDiff | 4.17 ± 2.93 | 6.17 ± 3.92 | 8.35 ± 2.86 | 4.70 ± 3.15 | 6.15 ± 2.67 | 9.70 ± 3.38 | 3.34 ± 2.93 | 5.69 ± 3.74 | 6.06 ± 3.99 | 6.10 | 0.003 | 0.115 |
| ALTeasy | 6.14 ± 1.59 | 6.79 ± 1.64 | 7.64 ± 1.16 | 6.35 ± 1.54 | 6.92 ± 1.03 | 7.52 ± 1.22 | 5.90 ± 1.43 | 6.60 ± 1.45 | 7.41 ± 1.08 | 0.36 | 0.834 | 0.008 |

Notes: MT - Memory Training, GC - Group Counseling, MoCA - the Montreal Cognitive Assessment, ALT – Associative Learning Test, ALTDiff - ALT difficult condition, ALVT – Auditory Verbal Learning Test.

Effects of memory training and the boost effects of group counseling

Regarding cognitive outcomes, ANOVA revealed significant Group × Intervention interactions in associative learning (Fig. 2, Table 3). Further analysis showed that, after memory training (post- minus mid-intervention), the GC group showed no significant improvement in ALT ($p = 0.08$, Cohen's $d = 0.26$) and ALTDiff ($p > 0.05$, Cohen's $d = 0.09$), while the MT group significantly increased performance in ALT ($p = 0.001$, Cohen's $d = 0.62$) and ALTDiff ($p < 0.001$, Cohen's $d = 0.68$), as well as the GC + MT group ($p < 0.001$, Cohen's $d = 0.96$ for ALT ; $p < 0.001$, Cohen's $d = 1.08$ for ALTDiff). Comparing to the CG group, two memory training groups showed enhanced memory performance. Compared with the MT group, the MT + GC group demonstrated greater memory improvements.

We further conducted a correlation analysis to validate the relationship between group counseling-related changes (mid- minus pre-intervention) and memory training-related changes (post- minus mid-intervention). Correlation analysis revealed a positive

correlation between the change scores in ATA and Digit Span Forward only in the GC + MT group ($r = 0.346$, $p = 0.049$) but not in the MT ($r = 0.146$, $p = 0.449$) or the GC groups ($r = 0.174$, $p = 0.325$).

Emotional improvements, memory training gains and amygdala-hippocampus connectivity

In brief, emotional improvements in anxiety and ATA were positively correlated with FC between the right amygdala and left hippocampus, and negatively correlated with FC between the right amygdala and right hippocampus.

The ROI-based analyses were performed to examine the correlation of amygdala-hippocampus connectivity with memory training gains. Results showed that FC between left hippocampus and amygdala positively correlated with improvements in Digit Span Forward when individual differences in emotional changes were controlled. The voxel-wised analysis validated the boost effect of amygdala-hippocampus connectivity on cognitive improvements. In addition, it also showed a negative relationship between ALT improvements and FC in right hippocampus and amygdala. However, this correlation was not significant when the individual differences in emotional changes were controlled. Detailed results are presented in Supplemental Materials (Results S1-S3).

These results suggested that counseling-induced emotional improvements manifested as changes in the amygdala-hippocampus pathway, in the meanwhile, changes in this pathway influenced memory training gains in older adults. It is noteworthy that functional separation was demonstrated in the FC between amygdala with left hippocampus and that with right hippocampus.

Discussion

This study examined whether memory training combined with group counseling aimed at alleviating depression and anxiety would produce greater training gains in older adults with memory complaints. The active-controlled randomized trial compared the combined intervention (GC+MT) group with memory training and group counseling groups. Results show that 3 sessions of group counseling decreased symptoms of depression and anxiety, maintained well-being, and promoted attitudes towards aging. Memory training enhanced performance on associative learning, in consistence with previous training [15,44–46] studies which reported individuals with SMC could benefit from cognitive training. More importantly, the GC+MT group demonstrated a larger improvement in memory (Cohen's $d = 0.96$) than memory training group (Cohen's $d = 0.62$), suggesting improved emotional states derived from group counseling boosted the effect of subsequent memory training. The present study expands previous multicomponent memory interventions by providing direct evidence supporting the synergistic effects of psychological intervention and memory training on cognitive outcomes. Our finding highlights the importance of treatment for negative emotional states correlated with subjective memory decline and the significance of promoting positive self-perception of aging. Integrating psychological intervention into traditional memory training may be promising to augment effectiveness on cognitive performance for older adults with SMC.

The present study also demonstrated that the boost effect of positive emotion on training benefits was related to the amygdala-hippocampus connectivity. The amygdala and hippocampus are the two fatal brain regions related to human emotion and cognition. Several imaging studies [17,47] found cognitive training was associated with hippocampal relevant regions. A study [46] using multidomain MRI scans found that resting-state connectivity between the right hippocampus and the superior temporal gyrus significantly differed between the pre- and post-test. Although episodic memory critically depends on the hippocampal complex, the amygdala is important for modulating the neural circuitry of episodic memory. Previous researchers [48,49] suggested that emotion through the amygdala's influence can alter three components of episodic memory: encoding, consolidation, and the subjective sense of remembering. Recent studies [50] also found that the emotional significance of the experience influenced the cognitive process, and emotionally arousing events were typically better remembered than neutral events. Through the amygdala-hippocampus circuit, negative emotions probably have an impact on cognitive process such as attention and perception [51], and alleviated depression and anxiety can facilitate a greater magnitude of cognitive training gains.

The present study confirmed the boost effect of improved mood on memory training from both behavioral and the cognitive neural perspectives. There are several strengths in the present study. First, by combining psychological intervention with cognitive training, we made the pilot experimental work to investigate whether improved emotional states would amplify efficacy of cognitive training, which helps to have a better understanding of the relationship between memory and emotion in individuals with SMC. Second, we used an active-controlled design, the intervention and control activities were matched in frequency, duration and format for both group counseling and memory training. It enabled us to control several potential confounding factors such as expectation effect, social interaction during group training and general cognitive stimulation of using tablets. Finally, we combined the behavioral and cognitive neural analyses to confirm the boost effect, which strengthened the reliability of the finding.

Some limitations also should be mentioned in the present study. The MT groups did not receive fMRI scanning which hindered to systematically compare intervention-induced functional changes among three groups. Further, as not all participants meet the requirements of MRI scanning, the sample of behavioral data and MRI data were not strictly matched, which might obstruct the interpretation of the results. Second, the duration of group counseling and memory training was relatively short, so it might limit emotional and cognitive benefits derived from the intervention. Third, no follow-up data was collected so we cannot evaluate whether the superior intervention effect in the combined group would be maintained. Fourth, 27 out of 124 participants at baseline withdrew during intervention. Although the attrition rate was comparable across three groups, decreased sample size reduced the power to detect small effect sizes on emotional and cognitive outcomes.

Conclusions And Implications

In conclusion, the present study show that memory training combined with group counseling for memory complaints-related depression and anxiety can induce larger memory gains than memory training or group counseling alone in older adults with SMC. It may be important to integrate treatment for depression and anxiety into cognitive training for older adults with memory complaints to achieve better intervention effect.

Abbreviations

SMC, subjective memory complaints; MT, memory training; GC, group counseling; ALT, Associative Learning Test; ATA, attitudes towards aging; FC, functional connectivity.

Declarations

Ethics approval and consent to participate

The protocol was approved by the Ethics Committee of the Institute of Psychology, Chinese Academy of Sciences (CAS). All participants provided written informed consent according to institutional guidelines.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by the National Natural Science Foundation of China (31600904), CAS Key Laboratory of Mental Health, Institute of Psychology (KLMH2020K03), Beijing Key Lab of Applied Experimental Psychology, Scientific Foundation of Institute of Psychology, Chinese Academy of Sciences (Y9CX191005), China Postdoctoral Science Foundation (2019M660849), and Beijing Postdoctoral Research Foundation (ZZ2019-26).

Authors' contributions

Study concept and design (Yin S, Zhu X, Li Juan), Acquisition of data (Yin S, Huo L, Ren W, Xiao Q, Lang M, Li Jin, Hou J, Niu Y), Analysis and interpretation of data (Yin S, Li R), Drafting of the manuscript (Yin S, Zhu X), and Critical revision of the manuscript for important intellectual content (Yin S, Zhu X, Li Juan).

Acknowledgements

Not applicable.

References

1. Jessen F, Amariglio RE, van Boxtel M, Breteler M, Ceccaldi M, Chételat G, et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 2014;10:844–52.
2. Jessen F, Wiese B, Bachmann C, Eifflaender-Gorfer S, Haller F, Kölsch H, et al. Prediction of dementia by subjective memory impairment: effects of severity and temporal association with cognitive impairment. *Archives of general psychiatry*. 2010;67:414–22.
3. Buckley RF, Ellis KA, Ames D, Rowe CC, Lautenschlager NT, Maruff P, et al. Phenomenological characterization of memory complaints in preclinical and prodromal Alzheimer's disease. *Neuropsychology*. 2015;29:571–81.
4. Fonseca JA, Ducksbury R, Rodda J, Whitfield T, Nagaraj C, Suresh K, et al. Factors that predict cognitive decline in patients with subjective cognitive impairment. *International psychogeriatrics*. 2015;27:1671–7.
5. Mol M, Carpay M, Ramakers I, Rozendaal N, Verhey F, Jolles J. The effect of perceived forgetfulness on quality of life in older adults; a qualitative review. *International journal of geriatric psychiatry*. 2007;22:393–400.
6. Perrotin A, La Joie R, de La Sayette V, Barré L, Mézenge F, Mutlu J, et al. Subjective cognitive decline in cognitively normal elders from the community or from a memory clinic: Differential affective and imaging correlates. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 2017;13:550–60.
7. Vannini P, Hanseeuw B, Munro CE, Amariglio RE, Marshall GA, Rentz DM, et al. Hippocampal hypometabolism in older adults with memory complaints and increased amyloid burden. *Neurology*. 2017;88:1759–67.
8. Stewart R, Godin O, Crivello F, Maillard P, Mazoyer B, Tzourio C, et al. Longitudinal neuroimaging correlates of subjective memory impairment: 4-year prospective community study. *The British journal of psychiatry : the journal of mental science*. 2011;198:199–205.
9. Rabin LA, Smart CM, Amariglio RE. Subjective Cognitive Decline in Preclinical Alzheimer's Disease. *Annual review of clinical psychology*. 2017;13:369–96.
10. Hyer L, Scott C, Lyles J, Dhaliwala J, McKenzie L. Memory intervention: the value of a clinical holistic program for older adults with memory impairments. *Aging & mental health*. 2014;18:169–78.
11. Kwok TC, Bai X, Li JC, Ho FK, Lee TM. Effectiveness of cognitive training in Chinese older people with subjective cognitive complaints: a randomized placebo-controlled trial. *International journal of geriatric psychiatry*. 2013;28:208–15.
12. Tsai AY, Yang MJ, Lan CF, Chen CS. Evaluation of effect of cognitive intervention programs for the community-dwelling elderly with subjective memory complaints. *International journal of geriatric psychiatry*. 2008;23:1172–4.
13. Barnes DE, Santos-Modesitt W, Poelke G, Kramer AF, Castro C, Middleton LE, et al. The Mental Activity and eXercise (MAX) trial: a randomized controlled trial to enhance cognitive function in older adults. *JAMA internal medicine*. 2013;173:797–804.

14. van Hooren SA, Valentijn SA, Bosma H, Ponds RW, van Boxtel MP, Levine B, et al. Effect of a structured course involving goal management training in older adults: A randomised controlled trial. *Patient education and counseling*. 2007;65:205–13.
15. Smart CM, Karr JE, Areshenkoff CN, Rabin LA, Hudon C, Gates N, et al. Non-Pharmacologic Interventions for Older Adults with Subjective Cognitive Decline: Systematic Review, Meta-Analysis, and Preliminary Recommendations. *Neuropsychology review*. 2017;27:245–57.
16. Engvig A, Fjell AM, Westlye LT, Skaane NV, Dale AM, Holland D, et al. Effects of cognitive training on gray matter volumes in memory clinic patients with subjective memory impairment. *Journal of Alzheimer's disease: JAD*. 2014;41:779–91.
17. Engvig A, Fjell AM, Westlye LT, Skaane NV, Sundseth Ø, Walhovd KB. Hippocampal subfield volumes correlate with memory training benefit in subjective memory impairment. *Neuroimage: Elsevier*; 2012;61:188–94.
18. Balash Y, Mordechovich M, Shabtai H, Giladi N, Gurevich T, Korczyn AD. Subjective memory complaints in elders: depression, anxiety, or cognitive decline? *Acta neurologica Scandinavica*. 2013;127:344–50.
19. Jorm AF, Christensen H, Korten AE, Jacomb PA, Henderson AS. Memory complaints as a precursor of memory impairment in older people: a longitudinal analysis over 7-8 years. *Psychological medicine*. 2001;31:441–9.
20. Fung AWT, Lee JSW, Lee ATC, Lam LCW. Anxiety symptoms predicted decline in episodic memory in cognitively healthy older adults: A 3-year prospective study. *International journal of geriatric psychiatry*. 2018;33:748–54.
21. Gatchel JR. Late-Life Neuropsychiatric Symptoms: Windows Into Cognitive Decline? *The American journal of geriatric psychiatry: official journal of the American Association for Geriatric Psychiatry*. 2020;28:72–4.
22. Li J, Nilsson LG, Wu Z. Effects of age and anxiety on episodic memory: selectivity and variability. *Scandinavian journal of psychology*. 2004;45:123–9.
23. Beaudreau SA, O'Hara R. Late-life anxiety and cognitive impairment: a review. *The American journal of geriatric psychiatry: official journal of the American Association for Geriatric Psychiatry*. 2008;16:790–803.
24. Petkus AJ, Reynolds CA, Wetherell JL, Kremen WS, Gatz M. Temporal dynamics of cognitive performance and anxiety across older adulthood. *Psychology and aging*. 2017;32:278–92.
25. Gulpers B, Ramakers I, Hamel R, Köhler S, Oude Voshaar R, Verhey F. Anxiety as a Predictor for Cognitive Decline and Dementia: A Systematic Review and Meta-Analysis. *The American journal of geriatric psychiatry: official journal of the American Association for Geriatric Psychiatry*. 2016;24:823–42.
26. Van der Mussele S, Fransen E, Struyfs H, Luyckx J, Mariën P, Saeuens J, et al. Depression in mild cognitive impairment is associated with progression to Alzheimer's disease: a longitudinal study. *Journal of Alzheimer's disease: JAD*. 2014;42:1239–50.
27. Phelps EA. Emotion and cognition: insights from studies of the human amygdala. *Annual review of psychology*. 2006;57:27–53.
28. Allen AP, Doyle C, Commins S, Roche RAP. Autobiographical memory, the ageing brain and mechanisms of psychological interventions. *Ageing research reviews*. 2018;42:100–11.
29. Small GW, Silverman DH, Siddarth P, Ercoli LM, Miller KJ, Lavretsky H, et al. Effects of a 14-day healthy longevity lifestyle program on cognition and brain function. *The American journal of geriatric psychiatry: official journal of the American Association for Geriatric Psychiatry*. 2006;14:538–45.
30. Valentijn SA, van Hooren SA, Bosma H, Touw DM, Jolles J, van Boxtel MP, et al. The effect of two types of memory training on subjective and objective memory performance in healthy individuals aged 55 years and older: a randomized controlled trial. *Patient education and counseling*. 2005;57:106–14.
31. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ (Clinical research ed)*. 2010;340:c332.
32. Montgomery P, Grant S, Mayo-Wilson E, Macdonald G, Michie S, Hopewell S, et al. Reporting randomised trials of social and psychological interventions: the CONSORT-SPI 2018 Extension. *Trials*. 2018;19:407.

33. Yu J, Li J, Huang X. The Beijing version of the Montreal Cognitive Assessment as a brief screening tool for mild cognitive impairment: a community-based study. *BMC psychiatry*. 2012;12:156.
34. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *The Gerontologist*. 1969;9:179–86.
35. Lam LC, Lui VW, Tam CW, Chiu HF. Subjective memory complaints in Chinese subjects with mild cognitive impairment and early Alzheimer's disease. *International journal of geriatric psychiatry*. 2005;20:876–82.
36. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior research methods*. 2007;39:175–91.
37. Xu S, Wu Z. The construction of "The Clinical Memory Test." [The construction of "The Clinical Memory Test."]. *Acta Psychologica Sinica*. 1986;18:100–8.
38. Maj M, Satz P, Janssen R, Zaudig M, Starace F, D'Elia L, et al. WHO Neuropsychiatric AIDS study, cross-sectional phase II. Neuropsychological and neurological findings. *Archives of general psychiatry*. 1994;51:51–61.
39. Gong YX. Manual of Wechsler adult intelligence scale-Chinese version. Changsha: Chinese Map. 1992.
40. Zung WW. A rating instrument for anxiety disorders. *Psychosomatics*. 1971;12:371–9.
41. Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. *Applied Psychological Measurement*. 1977;1:385–401.
42. Diener E, Emmons RA, Larsen RJ, Griffin S. The Satisfaction With Life Scale. *Journal of personality assessment*. 1985;49:71–5.
43. Lawton MP. The Philadelphia Geriatric Center Morale Scale: a revision. *Journal of gerontology*. 1975;30:85–9.
44. Kinsella GJ, Ames D, Storey E, Ong B, Pike KE, Saling MM, et al. Strategies for improving memory: a randomized trial of memory groups for older people, including those with mild cognitive impairment. *Journal of Alzheimer's disease: JAD*. 2016;49:31–43.
45. Nelson L, Tabet N. Slowing the progression of Alzheimer's disease; what works? *Ageing research reviews*. 2015;23:193–209.
46. Pike KE, Zeneli A, Ong B, Price S, Kinsella GJ. Reduced Benefit of Memory Elaboration in Older Adults with Subjective Memory Decline. *Journal of Alzheimer's disease: JAD*. 2015;47:705–13.
47. Lampit A, Hallock H, Suo C, Naismith SL, Valenzuela M. Cognitive training-induced short-term functional and long-term structural plastic change is related to gains in global cognition in healthy older adults: a pilot study. *Frontiers in aging neuroscience*. 2015;7:14.
48. Eichenbaum H, Fortin N. Episodic memory and the hippocampus: It's about time. *Current directions in psychological science*. SAGE Publications Sage CA: Los Angeles, CA; 2003;12:53–7.
49. Zola-Morgan S, Squire LR, Alvarez-Royo P, Clower RP. Independence of memory functions and emotional behavior: separate contributions of the hippocampal formation and the amygdala. *Hippocampus*. 1991;1:207–20.
50. Leal SL, Noche JA, Murray EA, Yassa MA. Age-related individual variability in memory performance is associated with amygdala-hippocampal circuit function and emotional pattern separation. *Neurobiology of aging*. 2017;49:9–19.
51. Anderson AK, Phelps EA. Lesions of the human amygdala impair enhanced perception of emotionally salient events. *Nature*. 2001;411:305–9.

Figures

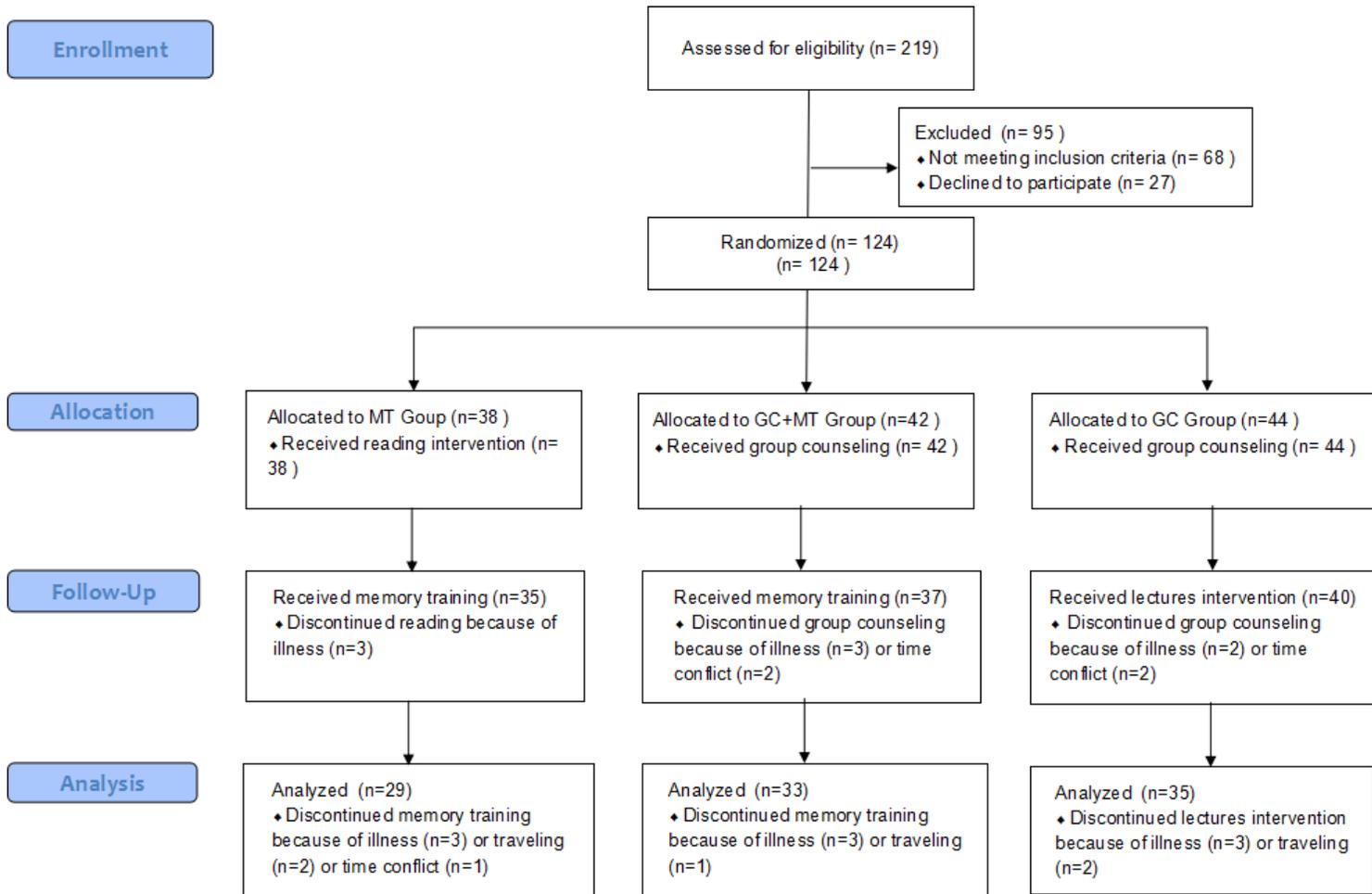


Figure 1

The flowchart of the trial. SMC: subjective memory complaints. MT: Memory Training. GC: Group Counseling.

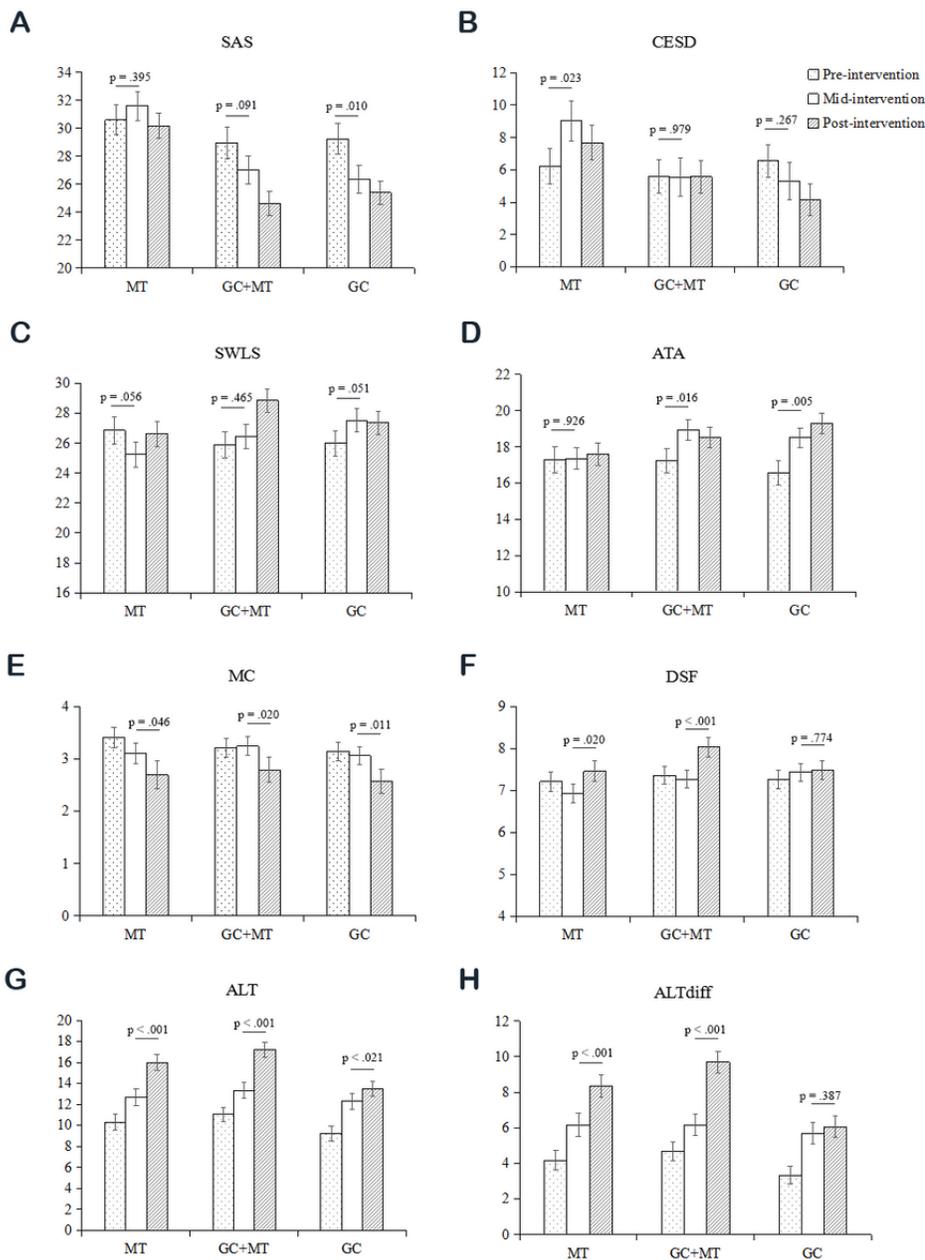


Figure 2

The effects of group counselling and cognitive training on emotional indicators and cognitive performance. Bar plots show the mean scores on anxiety (SAS), depression (CESD), subjective well-being (SWLS), attitudes towards aging (ATA), memory complaints (MC), digit span forward (DSF), associative learning (ALT) and associative learning difficult condition (ALTDiff) prior to and after intervention for the Memory Training (MT), Group Counseling (GC), and GC+MT groups.

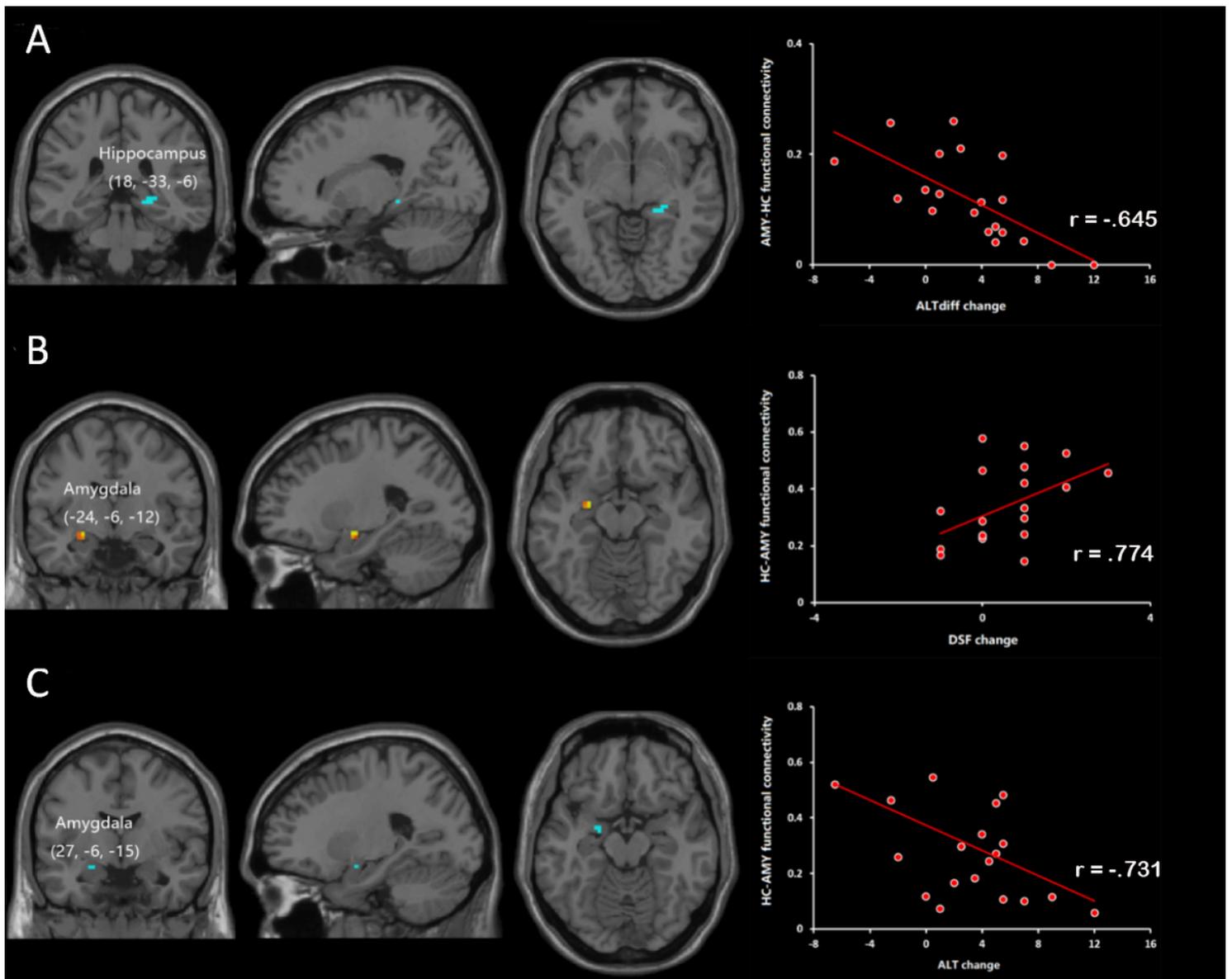


Figure 3

The boost effect of amygdala-hippocampus functional connectivity on cognitive improvements. Results showed significant correlation of : (A) ALTDiff changes with connectivity between right amygdala (peak MNI coordinate: 24, 0, -24) and right hippocampus (8 voxels; peak MNI coordinate: 18, -33, -6); (B) Digit Span Forward changes with connectivity between left hippocampus (peak MNI coordinate: -24, -15, -18) and left amygdala (7 voxels; peak MNI coordinate: -24, -6, -12); (C) ALT changes with connectivity between right hippocampus (peak MNI coordinate: 24, -30, -9) and right amygdala (5 voxels; peak MNI coordinate: 27, -6, -15) in the GC+MT group.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [CONSORTSPIChecklist.docx](#)
- [FigureS1.tif](#)
- [FigureS2.tif](#)
- [FigureS3.tif](#)

- [FigureS4.tif](#)
- [Supplementalmaterials.docx](#)