

Group- and Home-Based Cognitive Intervention for Patients with Mild Cognitive Impairment: A Randomized Controlled Trial

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Key Words

Brain-derived neurotrophic factor · Brain plasticity · Cognition training · Cognitive intervention · Mild cognitive impairment

Abstract

Background: We examined the efficacy of group-based cognitive intervention (GCI) and home-based cognitive intervention (HCI) in amnesic mild cognitive impairment (aMCI) and intervention effects on serum brain-derived neuro-

trophic factor (BDNF). **Methods:** In this randomized and rat-er-blinded trial, 293 patients with aMCI from 18 nationwide hospitals were randomized: 96 to the GCI group, 98 to the HCI group and 99 to the control group. For 12 weeks, subjects receiving GCI participated twice per week in group sessions led by trained instructors, and those receiving HCI completed homework materials 5 days per week. They were assessed at baseline, postintervention (PI) and at the 6-month

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follow-up after the intervention. The primary endpoint was the change from baseline to PI in the modified Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog). **Results:** In comparison to the controls (a 0.8-point decrease), the subjects receiving GCI (a 2.3-point decrease, $p = 0.01$) or HCI (a 2.5-point decrease, $p = 0.02$) showed significant improvements in the modified ADAS-Cog at PI, respectively. By the 6-month follow-up, those receiving GCI or HCI had better scores in the modified ADAS-Cog than the controls. The changes in BDNF levels significantly correlated with the changes in the modified ADAS-Cog in the GCI ($r = -0.29$, $p = 0.02$ at PI) and HCI ($r = -0.27$, $p = 0.03$ at 6-month follow-up) groups, respectively. **Conclusions:** The GCI and HCI resulted in cognitive improvements in aMCI. An enhanced brain plasticity may be a component of the mechanism underpinning the cognitive improvements associated with the cognitive interventions.

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Introduction

Mild cognitive impairment (MCI) has multiple etiologies and is categorized into amnesic (aMCI) and non-amnesic subtypes [1]. aMCI is considered a degenerative condition that may represent prodromal Alzheimer's disease (AD) [2, 3]. There are no pharmacological treatments to improve cognition or slow the disease progression in patients with aMCI [4]. It is important to develop treatment strategies for this population.

Numerous observational studies have found that rich social networking, high work complexity, mentally stimulating activities and physical exercise could delay dementia onset [5, 6]. Even at highly advanced ages, active engagement in mental, physical and social activities could postpone dementia onset by more than 1 year [6]. A previous study showed that memory training in subjects with MCI resulted in significant neural changes on functional brain imaging [7]. The result suggests that the brains of people with MCI may remain highly plastic; furthermore, cognitive intervention may be effective in MCI treatment.

Results of studies on cognitive intervention for aMCI were inconsistent [8, 9]. Objective and subjective measures of memory, quality of life (QOL) and mood have demonstrated significant improvements following cognitive intervention in half of the reviewed studies [8]. Although follow-up evaluations are important because aMCI is a degenerative condition in many individuals, they have not been conducted in many studies [8]. Further, most of the studies had a small sample size [8–10].

There is a lack of randomized placebo-controlled trials and standardization of training programs, with great variability in study design [8, 9]. The efficacy of cognitive intervention in MCI remains to be verified in quality trials in large samples.

Another limitation of past studies was the lack of inclusion of a biomarker that could provide mechanistic insight into the improvement in cognition in the cognitive intervention group. One plausible mechanism that may explain the cognitive improvement among people receiving a cognitive intervention is an increase in serum levels of brain-derived neurotrophic factor (BDNF). The role of BDNF has been shown in synaptic plasticity, dendritic remodeling, axon growth and neuronal survival [11]. Exercise increased levels of plasma BDNF [12] and induced BDNF-associated gene expression [13]. A recent study reported that computerized cognitive training increased serum BDNF levels in patients with heart failure [14].

The cognitive intervention programs of the previous studies were offered in groups or delivered in face-to-face individual sessions [8, 10]. The development of a home-based cognitive intervention (HCI) program for patients with MCI may be useful to those who have difficulty in regularly attending sessions at their local hospital and to those that are reluctant to take part in group-based classes. However, there have been no studies evaluating HCI for MCI. The aim of this study was to investigate the effect of group-based cognitive intervention (GCI) and HCI for patients with aMCI compared with control patients without cognitive intervention. Our hypothesis was that there would be differences in changes of cognitive function from baseline to postintervention (PI) assessments of a 12-week cognitive intervention between the GCI and control groups, and between the HCI and control groups. We also examined intervention effects on serum BDNF to explore mechanisms linking cognitive intervention with improved cognitive function.

Methods

Participants

Eligible patients were 50–85 years of age and had a diagnosis of aMCI according to the operationalized Petersen criteria [1], which included the following: a subjective memory complaint that was corroborated by an informant; objective memory decline, as defined by a delayed recall score of the Seoul Verbal Learning test worse than 1.0 standard deviations (SD) below age- and education-adjusted normative means [15]; normal general cognitive function, as defined by the Clinical Dementia Rating (CDR) scale of 0.5 [16], and a Mini-Mental State Examination (MMSE) score of more

than 1.5 SD below age- and education-adjusted normative means [17]; preserved activities of daily living (ADL), as defined by Seoul Instrumental ADL ≤ 7 [18], and a lack of dementia. All subjects had a Hachinski Ischemic Score ≤ 4 [19], brain MRI or CT showing no other diseases capable of producing cognitive impairment and a reliable informant who met the subject at least once a week and was sufficiently familiar with him/her to provide the investigator with accurate information. They could also read and write, which was assessed by the literacy test [20].

Subjects were excluded if they had any of the following: a severe or unstable medical disease that could interfere with successful completion of the study; a clinically significant laboratory abnormality, such as an abnormal thyroid function test, abnormally low levels of vitamin B₁₂ or folate, and positive syphilis serology; a primary other neurodegenerative or psychiatric disorder; drug or alcohol addiction during the past 10 years, or any hearing or visual impairment that could disturb an efficient evaluation. The doses of psychotropic medication or any drugs able to affect cognition were kept constant throughout the study period.

Study Design

This was a multicenter, randomized, rater-blinded, parallel-group study performed at 18 neurology clinics of nationwide hospitals in South Korea. The patients who had visited the clinics for memory decline and had been diagnosed as aMCI were consecutively recruited. They were randomly assigned in a 1:1:1 ratio to a GCI, HCI or control group by the block randomization method using SAS programming, stratified by the center. Therefore, there were subjects receiving GCI, those receiving HCI and control subjects in each center. The randomization sequence was known only to the clinical trial coordination center, which was contacted by the local principal investigator or coinvestigator at the participating center after enrollment of a patient. Treatment outcomes were assessed by raters who were unaware of the treatment group assignment. Subjects in the control group were informed that they would be able to participate in the cognitive intervention program after this study ended.

The study was performed in accordance with the International Harmonization Conference guidelines on Good Clinical Practice and was approved by the institutional review board of each center prior to beginning the study. Prior to participation in the study, all subjects gave their written informed consent to participate in the study. This study was registered at clinicaltrials.gov as NCT01358955.

Cognitive Intervention

Six neurologists and three neuropsychologists proposed potential programs from previously published or experiential-based programs. The programs were presented to a panel of dementia experts and were amended according to their suggestions. We applied the potential GCI program to 28 patients with aMCI and the potential HCI program to 88 patients with aMCI in a pilot study. The programs which were pitched at too high a level for aMCI were discarded or modified, resulting in the final version.

The GCI and HCI programs were conducted by trained health professionals (clinical neuropsychologists, occupational therapists and regular nurses). To standardize the training programs, we held a workshop to teach them how to apply the programs. The training manuals, demo videos, education resources (such as PowerPoint files and materials for GCI) and standardized home study materi-

als were also distributed. All subjects, including the controls, received an educational booklet regarding lifestyle for dementia prevention.

The GCI consisted of 90-min sessions twice weekly for 12 weeks, located in the hospital-based outpatient clinics. A group consisted of 5 subjects. The cognitive intervention was a comprehensive multimodal intervention, including multicomponent restorative cognitive training targeted largely at memory training and compensatory cognitive rehabilitation [21]. The following memory strategies were performed during memory training: categorization [22], story making [23, 24], visual imagery [23, 24], association [24], spaced retrieval [23, 24], saying something out loud to remember it [23], hierarchical organization [8], errorless learning [10], finding key words or the title of a story [10], face-name association [10], cueing [22], repetition [10, 23] and practice to fill in blanks and find incorrect points [10]. We also trained other functions, such as attention, executive function, language, orientation and visuospatial functions. The contents of the intervention program consisted of activities to improve ADL and providing knowledge for health and useful information for daily life (see online suppl. table S1; for all online suppl. material, see www.karger.com/doi/10.1159/000442261). This included pen and pencil training with visual and auditory materials. The program was conducted in a standardized manner. The difficulty level was adjusted according to the members of a group.

A welcome, reality orientation, reminiscence and talk were conducted for 10 min at the beginning of each session. For prospective memory training, an instructor told subjects what to do at break time or at a certain event. Subjects were to speak the task loudly and write it in a notebook. Next, verbal or visual memory training was conducted for 20 min. Training other cognitive domains for 15 min and recall training for 5 min followed. After a 10-min break, training other domains for 15 min and recall training for 5 min were repeated. Finally, they wrote or talked about the activities and memory strategies that were learned that day in a 10-min wrap-up. In the 1st and 13th sessions, a lecture about brain anatomy, memory functioning, and memory strategies and rehabilitation was delivered. In the last session, the patients discussed the most memorable activity from the sessions and reviewed memory strategies. Homework included writing a diary using a structured form.

Those participating in the HCI completed daily homework materials consisting of seven pages, 5 days per week, for 12 weeks. Six pages consisted of tasks for memory and other cognitive domains; the seventh page was a diary with the same structure used in the GCI. The daily homework material could be completed in approximately 30 min. Half of the homework material consisted of memory tasks and half consisted of other domain tasks. The content consisted of problem solving to improve ADL, knowledge regarding health and useful information for daily life (online suppl. table S2). The memory strategies that were applied in the GCI were also practiced with the homework materials [8, 10, 22–24]. The homework materials had high and low levels of difficulty. An instructor determined the level according to each subject's ability at baseline.

The participants visited a clinic every week in the 1st month and every other week in the 2nd and 3rd months. An instructor checked his/her homework and whether he/she remembered two memory strategies learned during the previous visit and had applied those in daily life. The subject did the remaining homework which had not been completed. Next, the instructor taught him/

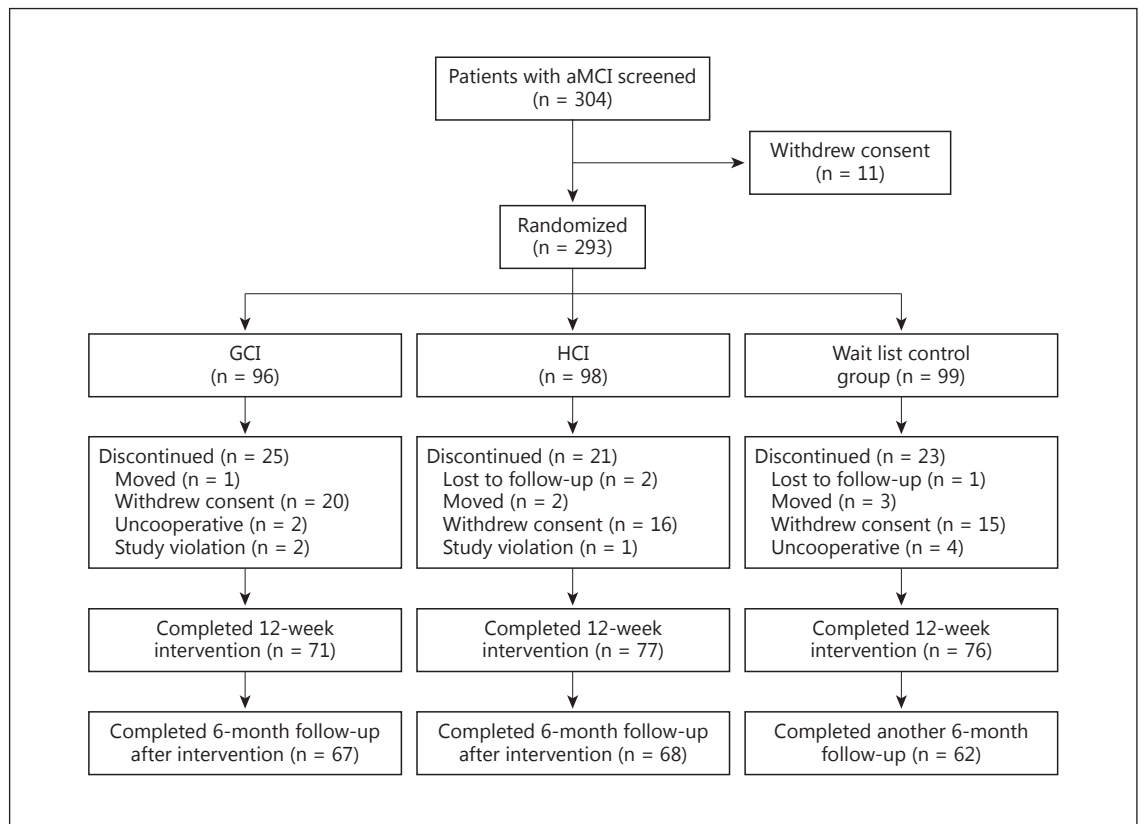


Fig. 1. Subject disposition in this multicenter, randomized trial to assess the efficacy of HCI and GCI programs in aMCI.

her two new memory strategies and how to complete the following homework assignment. The guidebook of homework materials was given to the informant to help him/her to complete it.

Outcomes

Assessments were performed at baseline, within 2 weeks after the last intervention (postintervention, PI) and at the 6-month follow-up. The primary efficacy outcome was the change from baseline to PI in the modified AD Assessment Scale-cognitive subscale (ADAS-Cog, range 0–89) [25]. Secondary outcome measures included the MMSE (range 0–30) [17], Digit Symbol Coding test (range 0–90), Stroop test (range 0–112), Animal Fluency, Controlled Oral Word Association Test (COWAT), story recall test [20], Forward Digit Span test (range 0–9), Backward Digit Span test (range 0–8), CDR-Sum of Boxes (CDR-SB, range 0–18) [16], 15-item version of the Geriatric Depression Scale (GDS-15, range 0–15) [26], Caregiver-Administered Neuropsychiatric Inventory (CGA-NPI, range 0–144) [27], Bayer ADL (range 1–10) [28], Prospective and Retrospective Memory Questionnaire (PRMQ, range 16–80) [29, 30], AD8 (range 0–8) [31], Prospective Memory Test (PMT, range 0–12) modified from the Royal Prince Alfred PMT [32], QOL-AD (range 0–52) [33] and Multifactorial Metamemory Questionnaire (MMQ)-Strategy subscale (range 0–76) [22, 34]. The PMT consisted of four tests regarding short- and long-term, and event- and time-based prospective memory. Increases in

scores represent improvement in the MMSE, Digit Symbol Coding test, color reading score of the Stroop test, Animal Fluency, COWAT, story recall test, Digit Span test, PMT, QOL-AD and MMQ-Strategy, and worsening for the modified ADAS-Cog, CDR-SB, GDS-15, Bayer ADL, CGA-NPI, PRMQ and AD8.

Measurement of Serum BDNF

Blood samples were collected at baseline and PI. They were collected in a serum separator tube and kept at room temperature for 30 min. The tubes were centrifuged for 10 min at 3,000 rpm. The serum was collected in an Eppendorf tube and frozen at $\leq -20^{\circ}\text{C}$. BDNF levels were measured via enzyme-linked immunosorbent assay (ELISA) using the Quantikine[®] ELISA human BDNF immunoassay kit (R&D Systems, Inc., Minneapolis, Minn., USA) according to the manufacturer's instructions.

Statistical Analysis

The primary null hypotheses were outcomes of no differences in the changes in the modified ADAS-Cog from baseline to PI between the GCI and the control group and between the HCI and the control group. Korean patients with aMCI had 27.6 ± 5.8 on the modified ADAS-Cog in the pilot study. We expected that meaningful treatment differences between each of the cognitive intervention groups and the control group might be ≥ 3 on the modified ADAS-Cog. Based on a 0.8 power to detect a significant difference

Table 1. Baseline characteristics and demographics of the subjects (per-protocol population)

	GCI group (n = 71)	HCI group (n = 77)	Control group (n = 76)
Age, years	70.8 (6.9)	68.5 (8.5)*	71.6 (6.5)
Female	50 (70.4%)*	50 (64.9%)	41 (53.9%)
Education, years	9.5 (4.8)	11.1 (4.1)*	8.8 (4.4)
AChEI medication	27 (38.0%)	27 (35.1%)	23 (30.3%)
APOE ε4 carriers	31/70 (44.3%)	29/76 (38.2%)	31/73 (42.5%)
MMSE score	25.9 (2.5)	25.9 (2.4)	25.3 (2.5)
Modified ADAS-Cog score	25.9 (6.6)	24.9 (6.8)	26.5 (6.6)
CDR-SB score	1.41 (0.96)	1.51 (0.95)	1.43 (0.78)
GDS-15 score	3.8 (3.0)*	4.5 (3.4)	5.4 (3.6)

Values are given as means (SD) or n (%). * $p < 0.05$ vs. the control group. AChEI = Acetylcholinesterase inhibitors; APOE = apolipoprotein E.

($p = 0.025$, double sided), 72 patients were required for each study group. Assuming a discontinuation rate of 23% [35], the sample size was 279, with 93 patients per group.

The logical memory score (range 0–50) was estimated by summing the scores of story immediate recall, story delayed recall and story recognition tests [20]. The executive function score was estimated by averaging the z scores from the Animal Fluency, COWAT, color reading score of the Stroop test and Digit Symbol Coding test [15]. The working memory score was estimated by averaging the z scores of forward and backward Digit Span tests. These z scores were based on the mean and SD of each measure in the age- and education-matched control group [36]. A z score is defined as where a score falls in the distribution of scores for normal subjects; a z score of +2.0 corresponds to a score that is 2 SD above the mean score.

The primary and secondary analyses at PI were performed in the per-protocol population. Demographic and clinical characteristics were compared using t tests for continuous variables and the χ^2 test for categorical variables. Changes at PI from baseline were compared using an analysis of covariance (ANCOVA) model, with the use of the baseline score as a covariate. The GDS-15 and sex, comparing the GCI and the control group, and age and education, comparing the HCI and the control group, were included as covariates. The long-term effects of cognitive intervention were analyzed in the per-protocol population who completed the 6-month follow-up, using repeated-measure ANCOVA. The Pearson correlation test was used to analyze associations among changes in BDNF levels and efficacy variables in each of the intervention groups. Significance for all tests was set at $\alpha = 0.05$ (two tailed). All statistical analyses were performed using SPSS 19.0 (SPSS, Chicago, Ill., USA).

Results

This study was conducted between May 2011 and January 2013. Between May 2011 and April 2012, 304 individuals were screened for eligibility. Eleven withdrew

their consent before baseline. Finally, 293 underwent randomization: 96 to the GCI group, 98 to the HCI group and 99 to the control group. Figure 1 shows the flow of subjects from the screening through the end of the study. The completion rates for the cognitive intervention over 12 weeks were 74.0 and 78.6% in the GCI and HCI groups, respectively. The retention rate at week 12 was 76.8% in the control group. The difference in discontinuation rates between the groups was not significant ($p = 0.75$). There were no significant differences in age, gender, education and scores of the MMSE, modified ADAS-Cog, GDS-15 and CDR-SB at baseline between the subjects who discontinued the study and those who completed it. The mean rate of attendance to the classes was 87.3% in the GCI group. The mean rate of homework completion was 95.3% in the HCI group. The baseline demographic and background characteristics of the efficacy population are summarized in table 1. The GDS-15 score was significantly lower and the proportion of female subjects was higher in the GCI group than in the controls. Those receiving HCI were significantly younger and more highly educated than the controls.

The results of the analyses of the efficacy variables at PI are shown in table 2. In comparison to the control group, those receiving GCI showed significant improvement in the modified ADAS-Cog (a 2.3-point decrease vs. a 0.8-point decrease in the controls, $p = 0.01$) and a tendency towards improvement in QOL-AD at PI. Compared with the control group, those receiving HCI showed significant improvement in the modified ADAS-Cog (a 2.5-point decrease vs. a 0.8-point decrease in the controls, $p = 0.02$), CDR-SB and QOL-AD scores at PI.

Table 2. Mean changes in efficacy measures from baseline to PI in the subjects receiving cognitive intervention and controls

	Baseline scores			Change from baseline to week 12				
	control group (n = 76)	GCI group (n = 71)	HCI group (n = 77)	control group (n = 76)	GCI group (n = 71)	p ^a	HCI group (n = 77)	p ^b
Modified ADAS-Cog	26.5 (6.6)	5.9 (6.6)	24.9 (6.8)	-0.8 (4.8)	-2.3 (4.6)	<i>0.01</i>	-2.5 (4.5)	<i>0.02</i>
Logical memory	16.2 (7.2)	18.5 (7.0)	18.8 (8.0)	1.8 (6.5)	2.3 (6.9)	0.23	1.3 (6.1)	0.66
Working memory	-0.05 (0.73)	-0.14 (0.77)	-0.25 (0.83)	0.05 (0.69)	0.07 (0.80)	0.65	0.09 (0.63)	0.85
Executive function	-0.81 (0.77)	-0.82 (0.63)	-0.91 (0.75)	0.18 (0.41)	0.16 (0.49)	0.54	0.22 (0.45)	0.69
PMT	5.6 (3.6)	5.2 (3.9)	5.5 (4.1)	0.3 (2.7)	1.2 (2.9)	0.08	0.8 (2.6)	0.16
MMSE	25.3 (2.5)	25.9 (2.5)	25.9 (2.4)	0.3 (1.8)	0.3 (1.8)	0.23	0.7 (2.0)	0.16
CDR-SB	1.43 (0.78)	1.41 (0.96)	1.51 (0.95)	0.03 (0.55)	-0.06 (0.68)	0.24	-0.21 (0.65)	<i>0.03</i>
AD8 (patient rating)	2.9 (2.1)	2.8 (1.7)	2.8 (1.7)	0.0 (1.8)	-0.4 (2.1)	0.28	-0.3 (2.1)	0.49
AD8 (informant rating)	2.8 (2.1)	3.1 (2.2)	3.1 (2.2)	-0.1 (1.6)	-0.8 (1.7)	0.11	-0.4 (1.8)	0.24
PRMQ (patient rating)	41.3 (13.9)	37.8 (10.6)	37.8 (10.7)	-1.1 (10.1)	-2.1 (7.9)	0.29	-2.1 (9.1)	0.25
PRMQ (informant rating)	36.8 (11.9)	39.8 (12.8)	40.0 (12.8)	0.6 (7.9)	-0.1 (8.1)	0.87	-0.9 (7.2)	0.12
MMQ-Strategy	29.8 (16.6)	26.8 (13.8)	26.9 (13.8)	1.7 (14.6)	3.7 (15.5)	0.54	1.8 (13.7)	0.44
GDS-15	5.4 (3.6)	3.8 (3.0)	4.5 (3.4)	-0.2 (2.9)	-0.4 (2.7)	0.11	-0.8 (2.5)	0.20
Bayer ADL	2.7 (1.3)	2.7 (1.3)	2.5 (1.3)	-0.1 (0.8)	-0.1 (1.2)	0.81	0.0 (1.0)	0.93
CGA-NPI	4.1 (5.3)	4.7 (8.4)	3.4 (4.9)	1.3 (9.1)	-1.8 (7.1)	0.07	0.9 (5.6)	0.45
QOL-AD	30.7 (5.3)	31.3 (4.3)	31.6 (4.7)	-0.3 (4.1)	1.1 (4.2)	<i>0.05</i>	0.9 (2.9)	<i>0.01</i>

Values are given as means (SD). Italics denote significance. ^a p values vs. controls by ANCOVA adjusted for covariates including sex, GDS-15 and baseline measures. ^b p values vs. controls by ANCOVA adjusted for covariates including age, education and baseline measures.

At the 6-month follow-up, those receiving GCI had better scores on the modified ADAS-Cog, PMT, AD8 (rated by informants) and CGA-NPI than the controls, and those receiving HCI had better scores on the modified ADAS-Cog and QOL-AD and a tendency towards improvement on CDR-SB than the controls (table 3; see also online suppl. fig. S1).

Changes in BDNF levels at PI versus baseline were as follows: a $706.1 \pm 6,280.0$ pg/ml increase in those receiving GCI, a $75.9 \pm 8,557.8$ pg/ml increase in the HCI subjects and a $970.5 \pm 8,788.3$ pg/ml decrease in the controls. The differences did not reach any statistical significance between the control group and each of the cognitive intervention groups. However, the changes in BDNF levels significantly correlated with changes in the modified ADAS-Cog ($r = -0.29$, $p = 0.02$) and MMQ-Strategy ($r = 0.29$, $p = 0.02$) at PI, and tended to correlate with changes in the modified ADAS-Cog ($r = -0.25$, $p = 0.05$) at the 6-month follow-up in the GCI group. The changes in BDNF levels also correlated with changes in the modified ADAS-Cog ($r = -0.27$, $p = 0.03$) and executive function score ($r = 0.30$, $p = 0.02$) at the 6-month follow-up in the HCI group.

Discussion

The GCI and HCI improved cognitive function on the modified ADAS-Cog as a primary efficacy assessment in aMCI compared to the controls. The benefits of cognitive intervention also persisted for at least another 6 months after it had been discontinued. The GCI and HCI mainly consisted of restorative cognitive training to utilize structured and repeated practice of specific cognitive tasks; in addition, they included compensatory cognitive training to teach strategies to compensate for cognitive impairments in daily function. The GCI also included education of healthy lifestyles and cognitive stimulation, such as reality orientation, reminiscence therapy and discussion. As confirmed in this study, comprehensive multimodal interventions that entail multiple approaches and target multiple cognitive domains may be the most promising in MCI, rather than focusing on one approach or one single domain [21].

The GCI subjects who received prospective memory training demonstrated significant improvement in actual performance on everyday memory, as indexed by the PMT. This improvement was replicated in AD8, an informant report of memory failures in everyday life. These

Table 3. Mean changes in efficacy measures from baseline to the 6-month follow-up after cognitive intervention in subjects with MCI and controls

		Change vs. baseline control group (n = 62)	Change vs. baseline GCI group (n = 67)	p value ^a		Change vs. baseline HCI group (n = 68)	p value ^b	
				between participants	within participants		between participants	within participants
Modified ADAS-Cog	week 12	-1.1 (5.1)	-2.2 (4.5)	0.03	0.09	-2.7 (4.5)	0.047	0.003
	week 36	-0.5 (5.2)	-2.3 (5.2)			-2.3 (6.1)		
Logical memory	week 12	1.5 (6.7)	2.6 (6.9)	0.12	0.65	1.7 (6.0)	0.59	<0.001
	week 36	4.6 (8.4)	5.7 (8.0)			4.2 (7.5)		
Working memory	week 12	0.03 (0.71)	0.11 (0.79)	0.44	0.63	0.09 (0.61)	0.70	0.12
	week 36	0.06 (0.66)	0.11 (0.74)			0.03 (0.59)		
Executive function	week 12	0.21 (0.41)	0.18 (0.50)	0.45	0.15	0.23 (0.44)	0.57	0.10
	week 36	0.26 (0.54)	0.20 (0.49)			0.21 (0.56)		
PMT	week 12	0.2 (2.9)	1.2 (2.9)	0.03	0.40	0.8 (2.6)	0.08	0.09
	week 36	-0.4 (2.7)	0.7 (2.9)			0.4 (2.6)		
MMSE	week 12	0.3 (1.8)	0.4 (1.8)	0.39	0.45	0.6 (2.1)	0.60	0.82
	week 36	0.3 (2.4)	-0.1 (2.3)			0.2 (2.3)		
CDR-SB	week 12	0.04 (0.60)	-0.07 (0.70)	0.12	0.67	-0.19 (0.62)	0.05	0.52
	week 36	0.15 (0.88)	0.04 (0.86)			-0.10 (0.67)		
AD8 (patient rating)	week 12	-0.2 (1.8)	-0.5 (2.0)	0.53	0.82	-0.5 (2.1)	0.14	0.14
	week 36	-0.3 (1.9)	-0.5 (2.0)			-0.6 (2.2)		
AD8 (informant rating)	week 12	-0.1 (1.6)	-0.8 (1.7)	0.03	0.40	-0.5 (1.8)	0.06	0.17
	week 36	-0.2 (1.7)	-0.7 (2.1)			-0.5 (1.8)		
PRMQ (patient rating)	week 12	-0.8 (10.3)	-2.2 (7.8)	0.11	0.19	-1.3 (8.4)	0.15	0.75
	week 36	-1.4 (12.1)	-2.6 (9.0)			-3.4 (8.0)		
PRMQ (informant rating)	week 12	0.9 (7.8)	-0.6 (8.2)	0.28	0.77	-1.1 (7.4)	0.06	0.43
	week 36	3.0 (10.2)	0.2 (9.2)			-0.4 (9.9)		
MMQ-Strategy	week 12	2.3 (15.1)	3.4 (15.4)	0.61	0.87	3.1 (13.4)	0.55	0.87
	week 36	-0.4 (15.4)	2.4 (14.8)			2.4 (11.3)		
GDS-15	week 12	-0.4 (3.0)	-0.5 (2.6)	0.24	0.78	-0.9 (2.3)	0.33	0.80
	week 36	-0.5 (3.3)	-0.1 (2.6)			-0.7 (2.5)		
Bayer ADL	week 12	0.0 (0.8)	-0.2 (1.2)	0.22	0.98	-0.0 (1.0)	0.71	0.59
	week 36	0.2 (1.2)	0.0 (1.1)			0.2 (1.3)		
CGA-NPI	week 12	1.6 (9.7)	-1.8 (7.4)	0.03	0.40	1.0 (5.7)	0.16	0.30
	week 36	1.5 (8.9)	-1.6 (8.8)			-0.6 (5.0)		
QOL-AD	week 12	-0.4 (4.3)	1.1 (4.2)	0.13	0.19	1.1 (2.6)	0.04	0.34
	week 36	-0.1 (4.7)	0.7 (3.6)			0.7 (3.3)		

Values are given as means (SD). Italics denote significance. ^a p values vs. controls by repeated-measures ANCOVA adjusted for covariates including sex, GDS-15 and baseline measures. ^b p values vs. controls by repeated-measures ANCOVA adjusted for covariates including age, education and baseline measures.

findings suggest that this GCI program is effective in improving retrospective and prospective memory in aMCI. Those receiving GCI demonstrated significant improvement in neuropsychiatric symptoms on the CGA-NPI. Similar results were found in a previous MCI study [37]. Targeting neuropsychiatric symptoms therapeutically may delay the transition to dementia [38]. CDR-SB is relatively sensitive in detecting some types of progression of MCI and has been used as a primary outcome measure-

ment tool in a drug trial for aMCI [25]. The HCI was superior to the control group at PI and the 6-month follow-up on the CDR-SB. Patients with MCI have reported a generally lower well-being score than elderly individuals without cognitive impairment [39]. Previous studies have reported a significant improvement in QOL in cognitive intervention groups [8]. In this study, the improvements in QOL were also observed in the HCI and GCI groups compared to the controls. Depressive symptoms had de-

creased significantly at the PI assessment or at the follow-up in the intervention group compared with the control group in some previous studies [8, 37, 40]. The antidepressant effect of a cognitive intervention was pronounced for patients with clinically relevant depressive symptoms at baseline [40]. The impact of cognitive intervention on depression might not have been significant in this study because the participants did not have relevant depressive symptoms at baseline.

In this study, BDNF serum levels were increased at PI compared to baseline in the cognitive intervention groups but decreased in the controls, albeit not significantly. However, the increments in BDNF levels significantly correlated with improvements on the modified ADAS-Cog and MMQ-Strategy in the GCI group, and with improvements on the modified ADAS-Cog and executive function scores in the HCI group. The findings imply that enhanced brain plasticity may be a component of the mechanism underpinning the cognitive improvements associated with cognitive intervention in aMCI. They also suggest that cognitive improvements in the GCI and HCI groups did not result from learning effects only. To our knowledge, this is the first time that changes in BDNF levels have been demonstrated in aMCI as a result of cognitive intervention.

We did not compare GCI and HCI in this study. We saw no reason to assume superiority of one intervention over the other. This was not the main focus of the trial. According to the characteristics of a patient and the training environment, GCI may be useful in some patients and HCI may be also useful in other patients. Our objectives were to compare cognitive function at PI between the GCI and the control group, and between the HCI and the control group. The GCI and HCI targeted the same cognitive domains and memory strategies, but the contents between GCI and HCI were not the same. The GCI and HCI consisted of the most appropriate contents in each setting of the intervention.

There are some limitations to our study. The first limitation regarding study design was that this was not double blinded but rater blinded. Subjects were instructed not to discuss their study involvement with the rater, but repeated follow-up assessments had the potential to influence the masking of assessment and introduce rater bias. Second, there were differences in age and education levels between the HCI and control groups; there were also differences in sex and the depression scale score between the GCI and the control group despite randomization. The variables were included as covariates in the analyses, but there is a possibility that the variables may affect the results. Third, di-

agnosis of aMCI was done clinically in this study. There might be a certain portion of healthy aged persons or subjects with aMCI due to other causes than AD. This might lead to false-positive results. Fourth, we did not assess adverse events during the cognitive intervention. Nonpharmacological interventions may also evoke side effects in participants [41]. They may become discouraged or depressed if they are confronted with their memory deficits in cognitive intervention. In order to avoid frustrating the participants, we adjusted the difficulty level of materials and assignments in GCI as well as HCI. Fifth, although there were no significant differences in age, gender, education, and scores of MMSE, modified ADAS-Cog, GDS-15 and CDR-SB at baseline between the subjects who discontinued the study and those who completed it, a dropout rate of 23.5% might lead to some bias. Out of those subjects who discontinued, only 4 could be recruited for a final assessment, and the results of the intent-to-treat population using the last-observation-carried-forward method were very similar to those of the per-protocol analysis. Therefore, we presented the results of the per-protocol analysis. Sixth, some of the secondary outcome measures had measured similar constructs. For example, several questions of AD8 and PRMQ measure similar cognitive dysfunction. It might inflate the α -error. Finally, the control group was not an active control, which was also a limitation. Both interventions included time with an instructor, which could provide a social benefit or some other confounding benefit to the intervention groups. The therapeutic effect of GCI and HCI may be affected also by nonspecific ingredients such as expectations, preferences, motivation and patient-doctor relationships [42].

The strengths of our study included a randomized trial of a relatively large sample size from nationwide centers and standardization of intervention programs for internal validity. The findings in this trial can be generalized to hospital clinics with trained instructors. HCI may promote broader access and participation. To the best of our knowledge, this study was the first to evaluate the effect of HCI on aMCI. In conclusion, GCI or HCI is effective in improving cognition in aMCI. The enhanced brain plasticity may be a component of the mechanism of the cognitive improvements associated with cognitive intervention.

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Disclosure Statement

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