ORIGINAL ARTICLE

Cognitive rehabilitation in patients with nonamnestic mild cognitive impairment

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Background: The nonamnesic type of mild cognitive impairment (na-MCI) is predementia state with subtle decline incognitive domains except memory. Although cognitive rehabilitation (CR) has been investigated in amnesic type of MCI, we could not find any trial that rehabilitated na-MCI exclusively. We studied the effectiveness of CR on na-MCI. **Materials and Methods:** This study was a blinded, randomized clinical trial. Individuals with age of 60 years or more, complete self-directedness and diagnosis of na-MCI, based on Neuropsychiatry Unit Cognitive assessment tool, were selected. The 51 patients were randomly assigned into three groups: CR, lifestyle (LS) modification, and the control group (CG). Neuropsychological tests for executive functioning were assessed at the baseline, after the interventions, and 6 months later. **Results:** The mean score of the "design fluency" test increased significantly in CR, compared to LS and CG ($P = 0.007$). In "five-point" test, mean score increased significantly in CR ($P = 0.03$). There was higher mean score of Behavioral Rating Inventory of Executive Function for adults in CR ($P = 0.01$). **Conclusion:** Consideration of the MCI subtypes allows us to target specific cognitive domains, such as information processing, for better CR outcome. CR may result in better performance of executive functioning of daily living.

Key words: Cognitive rehabilitation, mild cognitive impairment, nonamnestic

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INTRODUCTION

World's population is experiencing aging,[1] that leads to serious health, economic, political, and social complications. Degenerative process in aging usually affects cognitive state negatively. The cognitive decline may result in disrupted ability to work, live independently, or maintain normal social interaction, which finally will be diagnosed with dementia. It is expected that more than 16 million of elder adults will suffer dementia until 2050 in the United States. The cost of this developing trend in dementia will be more than 1 trillion dollars.[2]

Mild cognitive impairment (MCI) has been established as a transitional syndrome between normal cognitive state and dementia.[3,4] The reported prevalence of MCI in the elders has been 3–42%.[5] All of the cognitive domains including memory, language, visuospatial capacity, praxis, and executive function may be impaired by MCI. MCI can be divided into amnestic MCI (a-MCI) and nonamnestic MCI (na-MCI) depending on whether or not memory is impaired.[4,6] These subtypes are further subdivided into "single-domain" or "multi-domain," depending on the number of cognitive domains impaired.[7] Comprehensive diagnosis of MCI would be relied on low performances on at least two neuropsychological tests within a cognitive domain. Memory and executive functioning are considered the main cognitive domains for a-MCI and na-MCI, respectively.[8]

Many clinical trials have been proposed to decrease the progression of MCI to dementia with pharmacological

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or nonpharmacological interventions.[9,10] Pharmacological treatments, such as cholinesterase inhibitors, memantine, huperzine A, Vitamin E, and *Ginkgo biloba* did not show any benefits to decelerate progression of MCI into dementia.[9] Nonpharmacological interventions have been also taken into consideration because of lower side effects, patients' preference, and lack of effectiveness of the drugs. Change from a sedentary lifestyle to moderate physical activity has beneficial effects on cognitive functioning, and preliminary evidence suggests that such change may reduce the incidence of dementia.[10] Among the nonpharmacological therapies in MCI, cognitive rehabilitation (CR) has been highlighted.[11] CR is the process of relearning cognitive skills that have been lost due to brain impairment. If skills cannot be relearned, other capacities will be used to compensate the lost cognitive functions.[12] Some studies have shown that CR interventions may be effective on memory improvement in a-MCI, especially for compensatory strategies of prospective and episodic memory deficits.[13,14]

In many neurological conditions, CR has been shown to be effective on executive functioning, attention, and speed of information processing.[15-20] In multiple sclerosis, CR was effective on the speed of processing.[15,16] The effectiveness of CR in acquired brain injury was also reported.[17-19] CR was effective in mild to severe head trauma at any time after trauma.[19] CR also had positive effects on the function of the frontal lobe in patients with Parkinson's disease.[20]

To the best of our knowledge, all of the CR interventions have been designed for MCI as a single entity or for a-MCI as a specific subtype. We could not find any rehabilitation trial that was dedicated exclusively for na-MCI. Thus, we sought to evaluate the impact of CR on na-MCI.

MATERIALS AND METHODS

Study design and participants

This study was approved by the Ethics Committee and the Research Council of the Behavioral Sciences Research Center, Isfahan University of Medical Sciences. All study participants provided written informed consent before the evaluations. The experimental principles were in accordance with the Declaration of Helsinki. This was a blinded, randomized clinical trial. After the announcement about the screening of cognitive functioning for the retired staff of public schools in Isfahan, Iran, 213 persons agreed to be screened [Figure 1]. Through a semi-structured clinical interview, a neuropsychiatrist screened 213 participants. Individuals with the age of 60 years or more, at least 5 years of education, complete self-directedness in activities of daily living, lack of any active or history of major psychiatric and neurological disorders, and lack of any drug misuse were

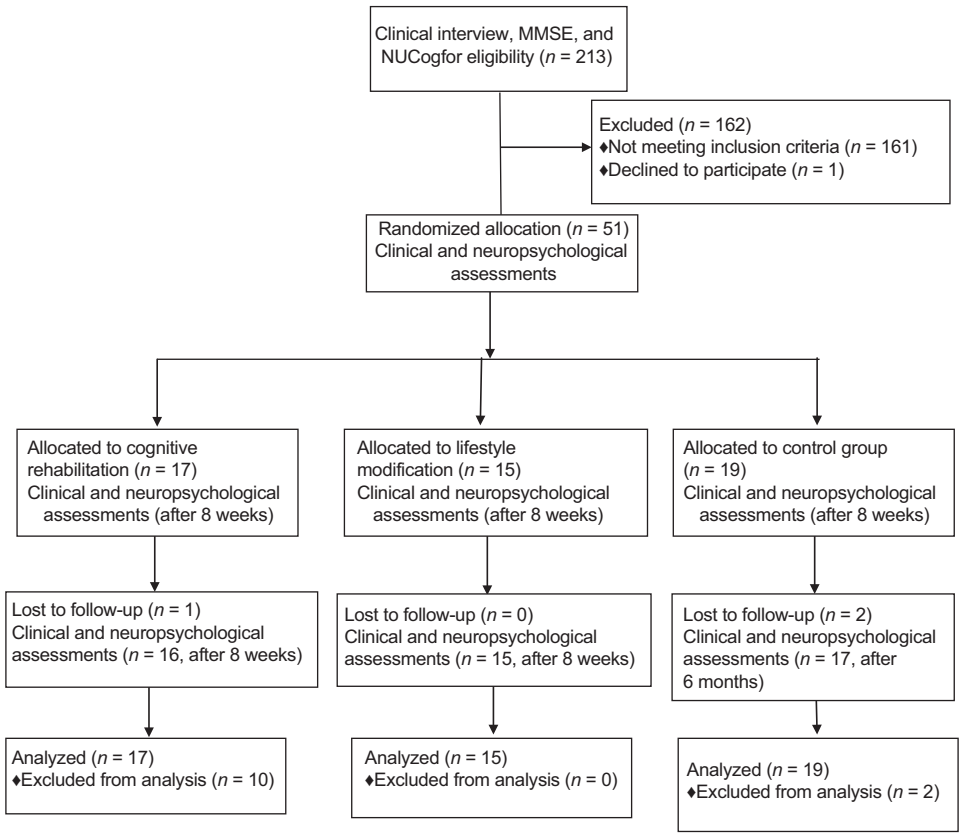

Figure 1: Study assignment and outcomes

screened for na-MCI. Patients with diagnosis of dementia and individuals who used medications that may affect cognitive state were excluded from the study. Based on the inclusion and exclusion criteria, 51 patients were recruited to this study. The participants were assigned into three groups using block-designed randomization that each block contained of three samples. Participants in the first group underwent "CR," the second trained for "Life Style" (LS) modification, and the third was "Control Group" (CG) who received only educational pamphlets after the end of the study [Figure 1]. Participants in each group were unaware of the existence of other groups. The baseline characteristics of the groups are presented in Table 1.

Neuropsychological assessments

Mini–mental state examination (MMSE) was used for all of the 213 participants to exclude patients with dementia.[21] The Neuropsychiatry Unit Cognitive assessment tool (NUCog) was selected to confirm MCI diagnosis.[22] It contains five cognitive domains of attention, visual-spatial, memory, executive function, and language, which has a maximum score of 20 for each domain. In the Persian version of NUCog, the cutoff point for separating MCI from normal individuals and patients with dementia are 86.5, 75, respectively.[23] Subjects with memory score of 16 or more in the memory subscale and 11 or less in the executive function subscale were considered as na-MCI.

Table 1: Demographic characteristics of the study participants in three groups

	n (%)			*P*
	CR group (*n*=17)	Life style modification group (*n*=15)	Control group (*n*=19)	
Gender				
Male	1 (5.6)	3 (20)	2 (10.5)	0.45
Female	16	12	17	
Education				
High school or less	8 (44.1)	4 (23.5)	7 (36.8)	0.59
University	9	11	12	
Diabetes				
Yes	6 (35.3)	2 (13.3)	5 (26.3)	0.36
No	11	13	14	
Hypertension				
Yes	7 (41.2)	6 (40)	5 (26.3)	0.58
No	10	9	4	
Ischemic heart disease				
Yes	2 (11.8)	1 (6.7)	3 (15.8)	0.71
No	15	14	16	
Hyperlipidemia				
Yes	6 (35.3)	3 (20)	7 (36.8)	0.52
No	11	12	12	
Hypothyroidism				
Yes	3 (17.6)	1 (6.7)	4 (21.1)	0.5
No	14	14	15	
Osteoarthritis				
Yes	3 (17.6)	4 (26.7)	6 (31.6)	0.62
No	14	11	13	
Insomnia				
Yes	2 (11.8)	1 (6.7)	1 (5.3)	0.75
No	15	14	18	
Chronic pain				
Ye	1 (5.9)	2 (13.3)	1 (5.3)	0.64
No	16	13	18	

CR = Cognitive rehabilitation

Widely accepted neuropsychological tests were selected as a battery to address executive function. The selected tests were: Tower of London (TOL) test to assess executive functioning, especially deficits in planning,[24] Color trail test (CTT) to measure remote divided attention and sustained attention,[24,25] Five-point test for figural fluency function to assess divergent thinking and shifting cognitive set,[24] Go-no go test for sustained attention and response control,[24] category fluency test to evaluate self-monitoring and working memory,[24] and design fluency test to measure cognitive flexibility and fluency in generation of visual patterns.[26]

Clinical assessments

The Mini International Neuropsychiatric Interview was used to rule out major psychiatric disorders.[27] General Health Questionnaire was also carried out to determine mental health state and individuals with scores lower than 22 were enrolled.[28]

The Behavioral Rating Inventory of Executive Function in Adults (BRIEF-A) was used to evaluate the behavioral aspects of executive functioning in daily living throughout this study.[29]

Health-promoting lifestyle profile test was used to measure the healthy-promoting behaviors' of lifestyle at 6 dimensions: Nutrition, exercise, health responsibility, stress management, interpersonal support, and self-actualization.[30]

Remediation programs

Cognitive rehabilitation group

Group sessions were conducted 2 h/week for a total of 8 weeks. The first session was dedicated to explain the basic elements of the protocol, obtaining information, and gathering participants' cognitive problems. All participants collaboratively agreed on symptoms of attention and executive functioning as the problem areas that they would like to manage better. The next three sessions were matched for the "attention process training" emphasized on direct attentional training that was a hierarchical treatment protocol.[31] The fifth and sixth sessions were matched for "goal management therapy" that used metacognitive strategies to improve patients' ability to organize and achieve goals in "real-life" situations. Participants learned how to use mindful attention

and goal setting to recognize and stop "absentmindedness" and "automatic pilot" to reduce daily errors and "slips."[32,33] The last two sessions dedicated to problem-solving therapy that facilitated identification of problems, awareness of various aspects of problems, generation of alternatives, initiation of action, and self-monitoring.[34,35]

Lifestyle group

Lifestyle modification has beneficial effects on quality of life, and preliminary evidence suggested that such change may reduce the incidence of dementia. However, its evidence on cognitive benefits toward more intellectual engagement has been insufficient.[10] Nutritional supplements to treat deficiency may improve cognitive performance, but supplements on top of a healthy diet cannot be recommended.[36] In the lifestyle modification group, discussion about theoretical and practical items for healthy LSs was explained. The role of physical activity in prevention of cognitive problem, importance of nutrition in preserving normal cognition, relation of biorhythms (especially quality and quantity of sleep) and cognition, impact of enriched social relationship in healthy aging, and role of stress in brain degeneration and stress management were explained during the eight sessions of LS group.

Procedure

Clinical interview and selection of eligible individuals were conducted by a neuropsychiatrist. Identified goals were selected by the research team and adapted operationalized rehabilitation protocol for CR was designed. Therapy was administered in a university clinic by a Ph.D. student in psychology who was well-trained in CR program, had a minimum of 10 supervised hours with adult rehabilitation clients, and completed an instructional program for using the materials. The rehabilitation tasks chosen for each session were specific to the participants' existing abilities and emphasize on the cognitive profile. There were written materials corresponding to specific topics that could be modified to match each participant's level of education and comprehension. Patients were given homework to practice the skills during the consequent week. They should practice homework and describe feedback in the next session. All participants were evaluated at the baseline, at the end of interventions 2 months later, and at the 6th month after the starting day by a trained resident of psychiatry (rater) with the neuropsychological and clinical assessment tools. The rater was unaware of the participants' allocation into the 3 groups. A well-trained psychiatry resident evaluated the participants with MMSE and NUcog. She was not aware of the participants' assignment or type of intervention.

Statistical analysis

The distribution pattern of the variables was checked in the study groups, using Shapiro test that supported normality. Leven's test and Box's test supported homogeneity of the variances and the covariances during follow-up times and between the groups, respectively. Demographic data were analyzed using one-way ANOVA. The repeated measures ANOVA used to compare "between and within subjects" effects. *Post hoc* analysis was done using Bonferroni test. The significance level was set at 0.05. All analysis was performed by intention to treat method. Statistical analysis was conducted using IBM SPSS Statistics 20.0 (IBM, Somers, USA) statistical software.

RESULTS

The average age of the study was 65.3 ± 4.8 years. The average age of LS, CR, and CG groups were 63.9 ± 4.0, 66.2 ± 5.5, 65.7 ± 4.7 orderly, which did not show any significant differences ($P = 0.37$).

Demographic characteristics of the three groups depicted in Table 1. In baseline, mean scores of NUCog were 78.4 ± 2.4, 79.0 ± 3.25, 79.7 ± 2.5 for CR, LS, and CG groups, respectively ($P = 0.37$).

Table 2 showed comparisons of mean scores of the neuropsychological and the clinical assessments between the three groups through repeated measures. The interaction effect between time and group effects was significant for BRIEF test ($P < 0.01$). This means that CR significantly increased the quality of executive functioning of daily living through the time of the study.

DISCUSSION

CR usually includes specific cognitive tasks or stimulus programs to improve current cognitive state or prevent more cognitive decline in MCI.[9-14] The previous studies revealed that cognitive training programs may improve memory performance.[37] However, there has been controversy about the effectiveness of rehabilitation on other cognitive domains except the memory.[37]

Many studies reported the effectiveness of CR for executive functioning in healthy elders, Parkinson's disease, multiple sclerosis, and traumatic brain injury.[15-20] Executive function is considered like a shelter which provides numbers of behavioral capabilities and related skills for better independent activities.[38] We proposed to evaluate the rehabilitation of executive function by "attentional training,"[31] "goal management therapy,"[32,33] and "problem-solving"[34,35] methods.

This study showed that in the field of information processing, the mean score of "design fluency" test increased significantly in CR, compared to LS and

Table 2: Comparisons between executive function tests in the three groups within follow-up times using analysis of covariance repeated measures

	Mean±SD			*P*	
	CR	Lifestyle modification	Control group	Follow-up*	Group effect**
Go/no-go					
Baseline	3±0	2.8±0.4	2.7±0.6	0.231	0.2
After 8 weeks	3±0	2.9±0.3	2.9±0.2		
6 months later	3±0	2.9±0.3	3±0		
Color trials test					
Base line	1.1±0.7	0.9±0.6	1.1±0.4	0.1	0.7
After 8 weeks	0.9±0.6	0.9±0.5	0.9±0.4		
6 months later	1.2±0.6	1.1±0.5	1.2±0.8		
Design fluency					
After 8 weeks	9.7±4.9	12.2±4	14±5.6	<0.001	0.007
After 8 weeks	12±4	17.2±4	16.5±8.8	*P* (1, 2)=0.001, *P* (1, 3)=0.001,	*P* (1, 2)=0.03, *P* (1, 3)=0.01,
6 months later	10.4±4.9	17±4.9	17.5±6.4	*P* (2, 3)=1	*P* (2,3)=1
Category fluency					
Base line	16±4.44	18.15±3.64	19.67±3.5	0.2	0.2
After 8 weeks	18.40±4.95	19.92±2.28	18.40±2.7		
6 months later	17.60±3.79	19.38±4.11	19.40±3.48		
Five point					
Base line	20.13±7.81	25.85±12.33	25.50±6.9	0.4	0.03
After 8 weeks	19.60±6.7	25.92±5.90	26.57±5.37		*P* (1,2)=0.1, *P* (1,3)=0.04, *P* (2,3)=1
6 months later	22±8.15	25.84±8.6	28±7.14		
Tower of London					
Base line	30.80±3.34	30.54±3.68	32.47±2.16	0.025	0.616
After 8 weeks	31.93±3.36	33.23±1.96	32.46±2.23	*P* (1, 2)=0.057, *P* (1, 3)=0.022,	
6 months later	32.73±3.05	32.76±2.00	32.86±1.92	*P* (2, 3)=1	
MMSE					
Base line	27.67±1.49	29±1.35	27.53±1.99	0.5	0.09
After 8 weeks	28.20±1.01	28.30±1.45	27.60±1.63		
6 months later	28±1.96	28.92±1.44	27.86±1.72		
Behavioral rating inventory of executive function in adults					
Base line	124.27±25.21	107.54±18.94	110.79±16.60	<0.001	0.145
After 8 weeks	116.20±24.86	102.23±22.92	103.57±12.41	*P* (1, 2) <0.001, *P* (1, 3)=0.001,	
6 months later	110.60±21.29	109.60±24.40	95.50±12.37	*P* (2, 3)=0.679	
Health promoting lifestyle profile test					
Base line	138.7±21.6	135.7±30.6	144.6±24.9	0.075	0.772
After 8 weeks	142.4±33.9	151.6±28.3	144.2±21.6		
6 months later	135.1±25.8	146.0±25.9	143.0±22.3		

*Time, 1 = Baseline, 2 = After 8 weeks of intervention, 3 = After 6 months, **Group, 1 = Rehabilitation group, 2 = lifestyle group, 3 = Control group, Comparison between paired groups were made with Bonferoni test. MMSE = Mini–mental state examination; CR = Cognitive rehabilitation; SD = Standard deviation

CG. This test is considered to address the assessment of problem-solving, planning, and organizing deals as parts of executive functioning. In "five-point" test, mean score increased significantly in CR compared to CG. This result also supported rising of information processing. Alternation in attention control, which includes supervisory processes, self-monitoring, and inhibition, was assessed by "category fluency" and "go-no go" test. The mean scores of category "fluency test" did not increased significantly following the interventions. However, an increasing trend in performance was seen in CR than the other two groups. The "go-no go" test did not reveal any differences between the 3 groups.

Similar interventions in Parkinson's disease and traumatic brain injury revealed improvement in attention control, especially inhibition and shift of attention.[18,20] However, in this study, CR did not improve attention control. It may due to the lesser impairment of attention inhibition in MCI.[39]

The CTT test that assesses flexibility and switching did not show any differences between the 3 groups. In a systematic

review and meta-analysis study about the effectiveness of computer-based cognitive training in MCI, CTT test results also did not show any effect.[40]

TOL test was used to assess goal setting including planning and problem solving. No differences between the three groups were recorded. However, "goal management therapy" were effective in traumatic brain injury.[19]

BRIEF-A is sensitive to measure subtle executive changes in MCI in real life.[29] The changes in the mean score of BRIEF-A showed improvement of subtle executive functioning in CR compared to LS and CG groups. Although many of the neuropsychological tests did not reveal any difference, it was noteworthy that improvement in activities of daily shown after rehabilitation. A systematic review on CR and cognitive training for early-stage Alzheimer's disease and vascular dementia showed conflicting result that rehabilitation interventions did not apply a significant effect on the daily life of patients with early-stage Alzheimer.[41]

Several studies pointed to the effectiveness of CR in younger patients with Parkinson's disease, multiple sclerosis, and head trauma.[15-20] For long-lasting functional benefits, any CR program needs to restore the neural connections that support the cognitive skills. In other words, brain neuroplasticity is an essential element for cognitive remediation. Considering the fact that neuroplasticity reduces with age,[6] patients with MCI, that usually are elders, may have less potential capacity to obtain changes in neuronal connections. This may explain the reason for less effectiveness of CR in MCI in comparison with other brain disorders.[41]

Awareness to cognitive deficits might increase the chance for recovery after rehabilitation interventions.[41] Thus, patients with na-MCI that have less insight into their decline of executive functioning (in comparison to a-MCI and insight to memory decline) may obtain less benefit from rehabilitation.[4,41]

The health-promoting lifestyle profile test did not show any effectiveness between the 3 groups. Similar studies revealed results with controversies.[36]

Strengths and limitations

The subjects of this study were selected from patients with na-MCI exclusively. To the best of our knowledge, this is the first study, which dedicated to CR interventions on na-MCI subtype. One of the strengths of this study was its design as a randomized, blinded clinical trial with CG. Various neuropsychological and clinical tools, which evaluated the many aspects of cognitive and behavioral functioning, were used. None of the cases took psychotherapeutic drugs or any agent for better cognitive performance.

The limitations of this study were low sample size, which did not permit generalization of the results. The follow-up period was relatively short for a longstanding condition such as MCI. Lack of brain imaging and other biomarkers to confirm the diagnosis of MCI was another limit. We administered same neuropsychological tests at baseline and at posttreatment, which might lead to learning effect. However, we tried to overcome this problem by considering the CG.

CONCLUSION

Consideration of subtypes in patients with MCI could allow us to target specific cognitive domains, increasing the likelihood of a positive response to cognitive remediation. In na-MCI, information processing would be selected as the probable target for effective rehabilitation programs. Although CR did not show prominent improvement in neuropsychological capacity, it could result in better performance of executive functioning of daily living.

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Conflicts of interest

There are no conflicts of interest.

AUTHORS' CONTRIBUTION

MB contributed in the conception of the work, conducting the study, supervision of data gathering, interpretation of the results, writing the manuscript, and revising the draft of the final version of the manuscript. MA contributed in the conception of the work, data gathering, and writing the manuscript. MT contributed in the conception of the work, planning the intervention, and supervision of the interventions performance. GE contributed in the performance of the interventions. MRM performed statistical analysis and interpretations of the results. All authors read and approved the final manuscript.

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