

Cognitive Remediation in Diabetics with Combining Mindfulness-based Relaxation and Transcranial Electrical Stimulation

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Abstract

Objective: The present research aimed to determine the pure and combined effect of both techniques of mindfulness based-relaxation (MBR) and Transcranial Electrical Simulation (tCES) on decreasing prospective and retrospective memory errors and failure of executive functions of patients with type 2 diabetes.

Method: The study is a randomized three-group double-blind clinical trial with repeated measures designs. The sample of the study consisted of 30 patients selected through convenience and purposive sampling method from Diabetes Association of Bonab city. The selected subjects were randomly assigned to the three groups of MBR, CES, MBR+CES; then they received interventions related to their group in 10 individual sessions. All patients were assessed by the Barkley Deficits in Executive Functioning Scale (BDEFS) and Prospective and Retrospective Memory Questionnaire (PRMQ) before and after the interventions, and one month after the interventions.

Results: The results of split-plot analysis of variance (SPANOVA) indicated the change of the mean of retrospective and prospective memory over time, and the change of prospective memory over time in different groups. The results of covariance analysis and the post hoc test of Ben Foruni indicated that in the follow-up phase, the prospective memory errors in the MBR+CES group were significantly lower than both the MBR and CES groups ($P < 0.05$).

Conclusion: The results of the study may provide many theoretical and practical implications for improving the cognitive function of type 2 diabetic patients following the MBR and CES therapeutic.

Keywords: Executive Functions, Memory, MBR, CES, Type 2 Diabetes.

Introduction

Type 2 diabetes mellitus is a common metabolic disorder in adults that causes insulin resistance or insufficient insulin to maintain normal glucose levels in the body, which is characterized by elevated levels of blood sugar (Cordova, 2011; Jeevitaa, Krishna, Kashinath, Nagaratna & Nagendra, 2014). One of the most important complications of diabetes mellitus is diabetic neuropathy that occurs both

at the peripheral level and in the central nervous system. The main features of neurological damage during diabetes are impaired cognitive functions, memory impairment, and decreased learning (Zenker, Ziegler, & Chrast, 2013). Oxidative stress causes neuronal damages in 60% of diabetic population (Maritim, Sanders & Watkins, 2003). In this relation, the cortex and hippocampus suffer from oxidative stress and lipid peroxidation caused by hyperglycemia more than other areas of the brain (Sytze, Cotter, Bravenboer & Cameron, 2013). Hyperglycemia is the most important cause of oxidative stress induction in diabetes and leads to excessive production of oxygen free radicals through enzymatic and non-enzymatic mechanisms (Maritim et al., 2003). Increased production

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of free radicals such as superoxide anion and subsequent activation of programmed cell death signals cause neuronal death in the brain tissue (Valko, Leibfritz, Moncol, Cronin, Mazur & Telser, 2007). Part of the neuronal damage in diabetes is also due to activation of the inflammatory system of the brain tissue and increased production of inflammatory and pro-inflammatory cytokines (Zenker et al., 2013). According to Biessels and Reijmer (2014), in patients with type 2 diabetes, abnormalities has also been observed in resting-state brain activity including a decrease in low frequency oscillations in post central gyrus and occipital cortex. Decreased brain activity in these areas is associated with poor memory function and executive function. Biessels and Reijmer (2014) also suggest that type 2 diabetes is associated with brain atrophy and increased burden of small-vessel disease, and decreased functional connectivity has been observed between these so-called default mode network regions, including the medial frontal gyrus, precuneus, and the medial temporal gyrus. The impaired default mode network connection is related to memory loss, executive function, and processing speed. On memory impairment in diabetic patients, in the Cameron et al.'s (2014) study, several MRI techniques have been used to characterize biochemistry and structure of the brain and the findings indicated that a history of hyperglycemia is associated with increased proliferation in the superior parietal lobule and hippocampus.

Due to the damage caused by diabetes in the brain areas related to memory and executive functions, two variables of daily memory and executive functions have been investigated as dependent variables in the study. Executive actions involve multiple cognitive processes that serve purposeful behaviors and actions (Chan, Shumb, Toulopoulou & Chen, 2008). Memory is one of the components of executive actions that enables the storage and manipulation of information in the mind (Rapport, Bolden, Kofler, Sarver, Raiker & Alderson, 2009). The action of this component (memory) is essential to facilitate the proper

functioning of other components of executive actions, and its proper function provides constant attention or focus, reflection on stimulus response, as well as inhibition of irrelevant impulses to the situation (Barkley, 2006). Memory has different types. In the present study, everyday memory, with emphasis on prospective and retrospective memory, has been studied. Retrospective memory and retrospective memory, which are respectively related to remembering past events, and our memory for specific actions at some times in the future, are important cognitive abilities and important everyday memory skills (Matthews & Bruno, 2011; Heffernan, O'Neill & Moss, 2011). It should be noted that retrospective memory errors can be considered as failures in encoding (Khan & Sharma, 2007), retrospective memory errors refer to the failure of the individual to recall the intentions. Zare, Alipour, and Mostafaei (2014) identify prospective memory as an important and pervasive aspect of out-of-laboratory memory that may be considered as one of the key factors in self-supporting and access throughout life.

Cognitive impairment affects daily life and professional and social interaction. Attention to cognitive rehabilitation has increased due to the limitations of drug therapies. Cognitive rehabilitation can have a positive effect on patients' memory performance (Mousavi, Zare, Etemadifar & Neshat Doost, 2018a). With regard to the daily functioning of each individual, memory and executive function are the most important cognitive domains. Therefore, paying attention to the repair, rehabilitation or reconstruction of these two important and essential abilities is crucial for the daily functioning of diabetic patients. According to the provided explanations, interventions that can modify the structure or function of the brain regions involved in memory and executive functions damaged or altered by diabetes, may reduce the psychological distress of patients and appear to improve diabetes control and cognitive function in diabetic patients. Since stress often causes alterations in sympathetic, parasympathetic balance, hypertension, heart rate,

vasoconstriction and peripheral blood vessels, and increased stress hormone production (Hannigan, 2013), therapeutic interventions that can reset the sympathetic-parasympathetic axis balance and reduce depression, stress, and anxiety, will be helpful. Among the interventions that, according to evidence, reduce depression, anxiety, and stress and also cause structural and functional changes in the brain, are yoga/meditation skills and techniques such as relaxation, breathing awareness, mindfulness, and cranial electrical stimulation techniques.

Therefore, one of the interventions of the study is mindfulness-based relaxation (MBR) intervention which is designed with adaptation to the strengths of relaxation techniques, along with breathing awareness and mindfulness. For an interesting link between respiration and brain, we refer to the study of Herrero, Khuvis, Yeagle, Cerf, and Mehta (2018) that, by employing direct intracranial recordings in humans, the brain limbic and cortical neuronal activity systems measured by intracranial electroencephalogram (iEEG) are linked to the breathing cycle. Previously, Loucks, Poletto, Simonyan, Reynolds, Ludlow (2007), and McKay, Evans, Frackowiak, and Corfield (2002), also suggested that automatic vegetative control of breathing could be stopped by higher cognitive factors. In 2012, Masaoka, Sugiyama, Katayama, Kashiwagi and Homma also claimed that the fact that breathing patterns in humans are affected by fear/anxiety is the indicative of involvement of the limbic and cortical centers in breathing. It is remembered that the MBR technique provides breathing awareness practices, breathing and exhaling awareness, and breath holding and regulating at all stages of muscle release. Relaxation technique reduces sympathetic nervous system activity and increases parasympathetic nervous system activity. The positive and therapeutic effects of relaxation techniques have been shown in various studies. For example, reducing pulse rate, situational anxiety, perceived stress, and salivary cortisol are shown in the studies of Lipschitz et al. (2013), Pawlow and Jones (2001), and anxiety

reduction following relaxation exercises in the studies of Javanmard and Mohammadi Garegozlo (2012) and Bonadonna (2003). Concerning the benefits of progressive muscle relaxation technique and its immediate results, Pawlow and Jones (2002) observed a significant decrease in salivary cortisol secretion by performing two laboratory sessions of muscle relaxation. Davison, Chensney, William, and Shapiro (2005) also introduce this method as one of the effective ways to deal with stressors and eliminate the undesirable physiological effects of stress. Another approach to reduce stress is mindfulness-based stress reduction (MBSR) technique. In particular, some researchers, including Jeevitaa et al. (2014), show that in people with diabetes compared to non-diabetics, the score of mindfulness scale is significantly low, and poor mindfulness is positively associated with chronic disease progression. In MBR technique, relaxation and breathing awareness practices are combined with mindfulness techniques and principles. On the positive effects of mindfulness, numerous studies have confirmed the participation of mindfulness interventions to regulate glucose in patients with diabetes (Loucks, Schuman-Olivier, Britton, Fresco, Desbordes, Brewer & Fulwiler, 2015; Weare, 2014; Crane, Kuyken, Hastings, Rothwell & Williams, 2010).

Other therapeutic techniques that can repair and reconstruct the structure and function of brain regions and have changed due to chronic diabetes and improve the accuracy and speed of diabetes treatment and cognitive function improvement in type 2 diabetes patients, trans cranial electrical stimulation technique (tCES) is also known as cranial electrical stimulation (CES) of the brain. This is a safe, painless, and noninvasive treatment technique that is widely used in clinical practice (Gong, 2016). Studies show that CES induces a mild stimulation in the hypothalamic brain region, leading to a balance in neurotransmitter activity (Ellsworth, 2012). In the study of Feusner, Madsen, Moody, Bohon, Hembacher, Bookheimer and Bystritsky (2012), electrical stimulation with pulse frequency of 0.5 and 100 Hz showed that CES

inactivated the cortex in the midline parietal and prefrontal regions. In addition, 100 Hz stimulation significantly alters the default mode network (DMN) communication. Therefore, CES appears to lead to similar cortical inactivation patterns for 0.5 and 100 Hz, and associate with a strong change in functional connectivity for 100 Hz stimulation. Therefore, as discussed above, CES with 0.5 and 100 Hz pulse frequency for 20 minutes was selected as another intervention of the study.

In summary, the present study selected two interventions of mindfulness-based relaxation (MBR) designed with the strengths of relaxation, breathing awareness, and mindfulness techniques, and trans cranial electrical stimulation (tCES) with a pulse frequency of 0.5 and 100 Hz as two treatment interventions in order to determine the pure and combined effects of these two therapies in reducing failure of executive function and daily memory errors in type 2 diabetes patients.

Methodology

The present study is a randomized three-group double-blind clinical trial. In terms of purpose, this study is an applied study, and in terms of implementation, it is a quasi-experimental research with repeated measures design. One of the most important biases in the design and implementation of a clinical trial is selection bias, in which using random selection is considered as a best way to reduce it. In this study, the type of treatment protocol was selected during the sampling phase by stratified random sampling (the number one, two, or three card was selected by the first subject of each group). That is, in the first session and at the first patient visit of each group, belonging to the treatment group was identified. Therefore, in the case of blindness, which is an important condition of clinical trial research, the study was conducted as a double blind study. The statistical population of the study consisted of all patients aged 25-55 years with Type 2 diabetes who were the members of Bonab Diabetes Association. The sampling method of the study was purposeful and convenience sampling. Thus, according to the inclusion and

exclusion criteria and the possibility of patients' participation in the research, 30 patients with type 2 diabetes were selected for participating in the study. Then, 30 selected patients by age, gender, and literacy matching were randomly assigned to the three groups of 10 individuals: 1) MBR group, 2) CES group, and 3) MBR+CES group. It should be noted that the patient selection and treatment providing lasted from winter 2018 to summer 2019. Also, in order to prevent the consequences of losing and dropping subjects, in case of dropping in each group, reselecting the patients was performed in order to have 10 patients in each group.

Inclusion and Exclusion Criteria

Inclusion criteria were having at least 3 years of Type 2 diabetes history, not receiving psychological treatments since diagnosis of the disease, having at least middle school education, aging between 25 to 55 years, ability to participate in therapy sessions, willingness to cooperate, and non-pregnancy and breast feeding while performing the research for female patients. Exclusion criteria included changes in drug therapy as recommended by the physician recommendation, reluctance to continue treatment, incidence of major stresses, and acute and unexpected events at each stage of the plan, nephropathy, retinopathy and serious neuropathy according to the diagnosis of a specialist physician, Acute psychiatric disease and drug therapy for it, having chronic illnesses such as cancer or other serious medical illnesses other than diabetes-related illnesses or diseases associated with diabetes, absence for more than 2 sessions, having pacemaker or defibrillator in the heart, and having a history of head and neck surgery or a history of severe head trauma in the last 6 months.

Ethical Considerations

- Before starting treatment, initially, informed consent was obtained from patients.
- The patients are assured that their names and other information will be kept confidential.
- The patients were given the right to be informed of the results of their tests if desired.

- At each stage of the study, the patients were excluded from the research process if they did not want to continue or experience acute stress.
- Intervention sessions were held 5 sessions daily (providing stimulation) and then 5 sessions a day in between (to keep the patient in a stable state) in order not to interrupt treatment interventions abruptly and to prevent patients with possible withdrawal symptoms (especially due to CES stimulation, which leads to pleasure and euphoria from hormonal and physiological changes).

Data Collection and Procedure

For collecting the data and conducting the research, about one week before the interventions, the members of all three groups were pretested for executive functions and daily memory. Then, the members of the three groups of MBR, CES, and MBR+CES received the group-related interventions in 10 individual sessions, 5 sessions daily (stimulation period), and 5 sessions a day in between (stabilization period). Patients in all three groups were examined for executive functions and daily memory up to one week after the end of the intervention (post-test) and one month after the last intervention (one-month follow up). In fact, the time interval between pre-test, post-test, and follow-up was considered one month.

Interventions

Mindfulness-based Relaxation (MBR): In this method, in the first session after “being in the present moment” and “sitting meditation” training, the participants were partly explained the theoretical basics of relaxation and breathing control techniques such as over-breathing, under-breathing, breathing awareness. Then, the participants were instructed on how to do the practices. In the second session, the subjects were seated on a relaxation sofa with a long back and preferably with closed eyes in order to start the practices. They were asked to focus on the muscles and the voice of the performer and for 5-10 seconds perform tension and contraction on the muscles named by the presenter when hearing the word “start” or “contraction”, and simultaneously

focus on the feelings created by tension and by hearing the word “release” try to release and relax the muscles for at least 30 seconds and focus on the created emotions. In this technique, due to the high importance of the breathing control, at all stages of “release”, they were asked to perform three-step exercises of breathing through the mouth in 7 seconds, holding breath for 7 seconds, and expiration through the mouth in 7 seconds with awareness and attention to the air in and out when inhaling and exhaling and its control, and paying attention to the movements of the chest and abdomen when inhaling and exhaling, and with each inhaling and exhaling, respectively, perform the inward relaxation and the outward tension practice. The exercises were conducted on 8 group of muscles (including the muscles of the hands, upper part of the hands, shoulders and neck, back and scapula, chest, involved in the three-step breathing exercise process, abdominal muscles, posterior and anterior muscles of the legs) with the supervision and guidance of the researcher (corresponding author). At the end of each session, to ensure that no residual tension remained in the muscles, the subjects were asked to perform a checkout process concurrent with executor commands at the same time as they were with their eyes closed.

Trans Cranial Electrical Stimulation (tCES) Technique

The treatment was performed by using the Canadian Oasis Pro device of Mind Alive Company. These tools are designed to help people adjust and modulate the level of excitement of their cerebral cortex, whether recovering lost functions or enhancing and improving functions (Siever, 2015). Sheldon and Mathewson (2018) have also used the battery stimulator Oasis Pro, Mind Alive of Canada. However, in their study of 10 Hz cathodic stimulation, no significant difference was found in target diagnosis between trans cranial electrical stimulation oscillations and sham. In the study, stimulation intensity was considered with pulse frequency of 0.5 and 100 Hz and 20-minutes sessions. In the first session, before stimulation, the

theoretical basics of electrical stimulation of the brain were partially explained to the patients. In the second to tenth sessions, the participants sat on a special sofa with a long back. The lobes of their both ears were cleaned and damped with alcohol swab. Then, 2 clipped electrodes were inserted into the patient's right and left ear lobes. Then, the brain was affected by the electrical current through the electrodes placed on the ears. At CES, the pulsed current is bilateral and it does not matter which electrode is attached to which ear, but according to the Canadian Mind Alive company, the red electrode was connected to the right ear and the black electrode to the left ear.

It should be noted that the intervention method for the MBR+CES experimental group was that in this group both interventions were provided simultaneously to the patients. Thus, as the electrodes were plugged in to the patients' ears and electrical stimulation was performed, the patients also performed MBR practices under the supervision of the researcher.

Instrumentation

Barkley Deficits in Executive Functioning Scale (BDEFS)

The questionnaire was designed and developed by Barclay (2012) which has five subscales: time management, self-management/problem solving, self-restraint, self-motivations, self-regulation of emotion. The high scores on each scale can be indicative of a defect in that domain of executive function in daily activities. One of the primary purposes of interpreting each scale in a clinical report is based on its sub-scale face validity (Barclay, 2012). This tool has been standardized in Iran by Mashhadi et al. (2015). In their study, the Cronbach's alpha coefficient for this instrument was .91 (as cited in Oraki, Faraji, Zare, & Najati, 2018).

Prospective and Retrospective Memory Questionnaire (PRMQ)

It is a paper-and-pencil test, developed by Crawford et al. in 2003, with 16 questions and the subject

answers each question based on a five-point likert scale. This tool has one main sub-scale called retrospective/prospective memory and two sub-scales along with the main sub-scale called short-term/long-term memory and person-centered/peripheral memory. And finally, it has a general scale called general-daily memory, which is derived from the sum of the scales. This test basically shows the total memory error rate and its subscales. Crawford et al. (2003) reported the reliability of the test by internal consistency (Cronbach's alpha) in prospective, retrospective, and general scale (general memory) as .80, .84, .89, respectively (Zahednezhad, Poursharifi, & Babapour, 2012). The questionnaire has been standardized in Iran by Zare, Alipour, and Mostafaie (2014) and its desirable reliability and validity have been demonstrated. In the study of Zare et al. (2014), Cronbach's alpha coefficient for the whole questionnaire was .83.

Mindfulness-based Relaxation (MBR) Technique Book

The protocol presented in the study is designed for the MBR therapeutic technique based on the book of *Theoretical and Practical Guide to the Mindfulness-Based Relaxation Technique* developed by Mohammadi Garegozlo (2019). The protocol included training being in the present moment, sitting meditation training, teaching the theoretical basics of relaxation and breathing control techniques, and training on how to perform eight practices on the muscles. The explanation of how MBR sessions are conducted is described in detail in the interventions section of this article.

Oasis Pro Device

The Canadian Mind Alive device is designed and developed for clinical use of cranial electrical stimulation tDCS using the latest safety standards. It is the only device that offers the possibility of CES and MET intervention in addition to the tDCS capability. In CES, electrical current affects the brain through 2 clipped electrodes located in the patient's right and left ear lobes. This device provides cranial electrical stimulation by

TABLE 1. Descriptive statistics of age, three-month blood sugar (A1c), gender, literacy, and the results of one-way ANOVA, X², and Cramer's V, respectively, to compare these variables in the groups

Variable	MBR Group		CES Group		MBR+CES Group		Statistics
	(N=10)		(N=10)		(N=10)		
Age	40±9.6		45.5±9.4		43.20±8.9		F _{2,27} =0.89, P=.428
A1c	9.11±3.20		8.84±2.03		9.59±2.6		F _{2,27} =0.20, P=.820
Gender	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	X²=0.48, P=.787
Male	2	20	1	10	2	20	
Female	8	80	9	90	8	80	
Literacy	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	V=0.13, P=.910
Below Diploma	5	50	4	40	3	30	
Diploma	3	30	4	40	5	50	
University	2	20	2	20	2	20	

generating dipolar, asymmetric, and rectangular waves with frequency of 0.5 Hz and a current intensity consistently adjusted between 10 μ A and 500 μ A (Gong et al., 2016).

Results

Table 1 shows the mean and standard deviation of age, three-month blood sugar (HbA1c), gender, and literacy distribution in the groups.

According to the results of one-way analysis of variance (ANOVA), Chi-squared test (X²), and Cramer's V (Table 1), the compared groups were matched for age, three-month blood sugar (A1c), gender distribution, and literacy status (P> .05).

According to Table 2, a decreasing trend is observed in the mean scores of executive functions, and prospective and retrospective memory across the three groups. To examine the significance of observed reduction, since the study has both an

inter-subject design (comparing the three types of interventions) and an intra-subject design with repeated measurements (comparing the subjects at three time intervals), inter-intra-subject split-plot analysis of variance (SPANOVA) has been performed on a general linear and single-variant model (once for executive functions, once for prospective memory, and once for retrospective memory), but the results are presented in common tables.

The important assumptions were examined before performing the inter-intra-subject split-plot analysis of variance. The default normality of the observations by performing Shapiro-Wilk's test also showed the distribution of group scores normal in executive functions, prospective memory, and retrospective memory in all three stages of pre-test, post-test, and follow-up (P> .05). the results of Box's M test for examining the assumption of

TABLE 2. Mean and standard deviation of executive functions, and prospective and retrospective memory scores by group and stage

Variable	Group	Pre-test		Post-test		Follow-up	
		M	SD	M	SD	M	SD
Executive Functions	MBR	137.30	21.55	135.80	20.8	135.40	23.45
	CES	136.90	27.03	136.30	27.7	135.60	29.14
	MBR+CES	136.40	19.13	134.40	19.37	133.90	20.22
Prospective Memory	MBR	19.20	4.13	18.50	3.57	18	3.83
	CES	21.30	2.49	20.20	2.20	19.50	2.37
	MBR+CES	21.50	3.78	18.70	2.91	17.50	2.72
Retrospective Memory	MBR	19.80	4.29	19.10	3.81	18.80	4.56
	CES	20.90	3.25	20.30	2.36	19.50	4.01
	MBR+CES	19.40	2.72	17.70	2.71	16.70	2.45

TABLE 3. Mauchly's test for evaluating the same observational difference at different stages

Intra-Group Effects	W		df	Sig.	Epsilon		
	Mauchly	X ²			Greenhouse-Geisser	Huynd-Feldt	Lower Limit
Executive Functions Over Time	0.94	1.67	2	.434	0.94	1	0.50
Prospective Memory Over Time	0.97	0.86	2	.651	0.97	1	0.50
Retrospective Memory Over Time	0.88	3.26	2	.196	0.89	1	0.50

homogeneity of covariance variance matrices, confirmed the consistency of variance-covariance matrices in all three dependent variables; executive functions ($F_{M_{box}} = 1.59$, $P = .085$), prospective memory ($F_{M_{box}} = 0.56$, $P = .871$), and retrospective memory ($F_{M_{box}} = 0.76$, $P = .688$). The Leven's test results also confirmed the equalization of error variances in pre-test of executive functions ($F_{2,27} = 1.30$, $P = .289$), post-test of executive functions ($F_{2,27} = 1.99$, $P = .155$), follow-up of executive functions ($F_{2,27} = 1.21$, $P = .315$), prospective memory pretest ($F_{2,27} = 1.88$, $P = .172$), prospective memory posttest ($F_{2,27} = 2.78$), $P = .080$), prospective memory follow-up ($F_{2,27} = 2.01$, $P = .153$), retrospective memory pretest ($F_{2,27} = 0.51$, $P = .605$), post-test retrospective memory ($F_{2,27} = 1.14$, $P = .336$), and retrospective memory follow-up ($F_{2,27} = 0.94$, $P = .404$). In addition to the above assumptions, a univariate method requires the assumption of sphericity. Based on the results of a Mauchly's one-variable test in Table 3, the sphericity assumption of the covariance variance matrix is confirmed for the data of the present study ($P > .05$).

Then, after ensuring the test hypotheses, the results of SPANOVA were analyzed. The results of multivariate tests were evaluated in order to

examine the sameness of the means. Significance of the Wilks' lambda test indicated that there is no significant change in executive functions over time ($\lambda = 0.81$, $F_{2,26} = 3.007$, $P = .067$, $\eta^2 = 0.18$), and over time in the groups ($\lambda = 0.97$, $F_{4,52} = 0.18$, $P = .948$, $\eta^2 = 0.014$). That is, none of the therapeutic interventions have been able to reduce the failures of executive functions. There is significant change in prospective memory errors over time ($\lambda = 0.38$, $F_{2,26} = 20.930$, $P < .001$, $\eta^2 = 0.62$), and over time in the groups ($\lambda = 0.68$, $F_{4,52} = 2.74$, $P = .038$, $\eta^2 = 0.17$). Also, retrospective memory errors changed significantly over time ($\lambda = 0.66$, $F_{2,26} = 6.68$, $P < .01$, $\eta^2 = 0.34$). But the decrease in retrospective memory over time was not dependent on the groups and treatment interventions ($\lambda = 0.90$, $F_{4,52} = 0.69$, $P = .600$, $\eta^2 = 0.05$). An overview of intra-group (time) and inter-group (intervention type) effects is presented in Table 4.

According to the results presented in Table 4, the decrease in the failure of executive functions is not significant. However, there was a significant change in the mean of prospective memory errors over time ($F = 24.4$, $P < .001$) and over time in the groups ($F = 3.42$, $P < .05$). The mean of retrospective memory errors also decreased over time ($F = 7.57$,

TABLE 4. The results of inter- and intra-group effects

Variable	Source of Changes	Sum of		Mean		Effect Size	Test Power
		Squares	df	Squares	F		
Executive Functions	Time	57.62	2	28.81	2.9	.064	0.09
	Time and Group Interaction	5.91	4	1.48	0.15	.963	0.01
	Error (time and Group Interaction)	536.47	54	9.93			
Prospective Memory	Time	84.36	2	42.18	**24.4	< .001	0.47
	Time and Group Interaction	23.64	4	5.91	*3.42	.015	0.20
	Error (time and Group Interaction)	93.23	54	1.73			
Retrospective Memory	Time	43.80	2	21.90	**7.57	.001	0.22
	Time and Group Interaction	8.60	4	2.15	0.74	.567	0.05
	Error (time and Group Interaction)	156.27	54	2.89			

* $P < .05$, ** $P < .01$

TABLE 5. Covariance analysis of prospective memory scores at posttest and follow-up after adjusting for pretest effect

Variable	Source of Changes	Sum of		Mean		Sig.	Eta Squared
		Squares	df	Squares	F		
prospective memory posttest	prospective memory pretest	178.79	1	178.79	**83.9	< .001	0.76
	Groups	16.01	2	0.007	*3.76	.037	0.22
	Error	55.41	26	2.13			
	Total	11234	30				
Prospective Memory follow-up	prospective memory pretest	168.89	1	168.89	**54.8	< .001	0.68
	Groups	29.51	2	14.75	*4.79	.017	0.29
	Error	80.10	26	3.08			
	Total	10354	30				

*P<0.05, **P<0.01

P< .001). However, this decrease was similar in the three groups (F= 0.74, P= .567). Since the rate of prospective memory changes over time was not the same in the three groups, to compare pair means in terms of time and group, considering prospective memory pre-test scores as a covariance variable, analysis of covariance was performed for posttest and follow-up scores of prospective memory (Table 5).

According to Table 5, the results of covariance analysis, after controlling for the effect of prospective memory pretest, indicate that the mean of prospective memory in the groups at the posttest and follow-up stages is not the same. Even, the effect size (Eta squared) at the follow-up (.29) is larger than the post-test (.22). That is, the prospective memory errors were lower in the follow-up than in the post-test.

Table 6 shows the differences between the pair groups in both post-test and follow-up stages. According to the observations, there was no significant difference in the mean difference

between the groups at the post-test stage. But at follow-up, the prospective memory errors in the MBR+CES group were significantly lower than both the MBR and CES groups (P<.05).

Three diagrams in Figure 1 show the mean scores of the dependent variables in the three groups of MBR with blue graph, CES with green graph, and MBR+CES with yellow graph, in three stages of pre-test, post-test, and follow-up. Due to the downward trend in the graphs of all three variables, there is a tendency to decrease the mean of failures of executive functions, prospective memory and retrospective memory errors in all three groups. However, this decrease is significant only for prospective memory and retrospective memory has been seen in favor of combined therapy of MBR+CES. The interesting point about the charts is that for the CES group, the slope of the graph between the post-test phase and the follow-up phase is steeper than the pre-test to post-test phase. This suggests that the CES intervention will be more effective after a while so that the memory

TABLE 6. BonFerroni post hoc test for comparing the prospective memory in the groups at different stages (group and time interaction)

Variable	Stages	Group	Group	Mean Difference	Standard Error	Significance Level	Confidence Interval	
							Lower Limit	Upper Limit
Prospective Memory	Post-test	MBR	CES	-0.17	0.67	1.000	-1.89	1.55
			MBR+CES	1.47	0.68	.118	-0.26	3.21
		CES	MBR+CES	1.64	0.65	.055	-0.026	3.32
	Follow-up	MBR	CES	-0.016	0.81	1.000	-0.09	2.06
			MBR+CES	*2.125	0.82	.045	0.040	4.21
		CES	MBR+CES	*2.14	0.78	.034	0.13	4.15

*P<0.05

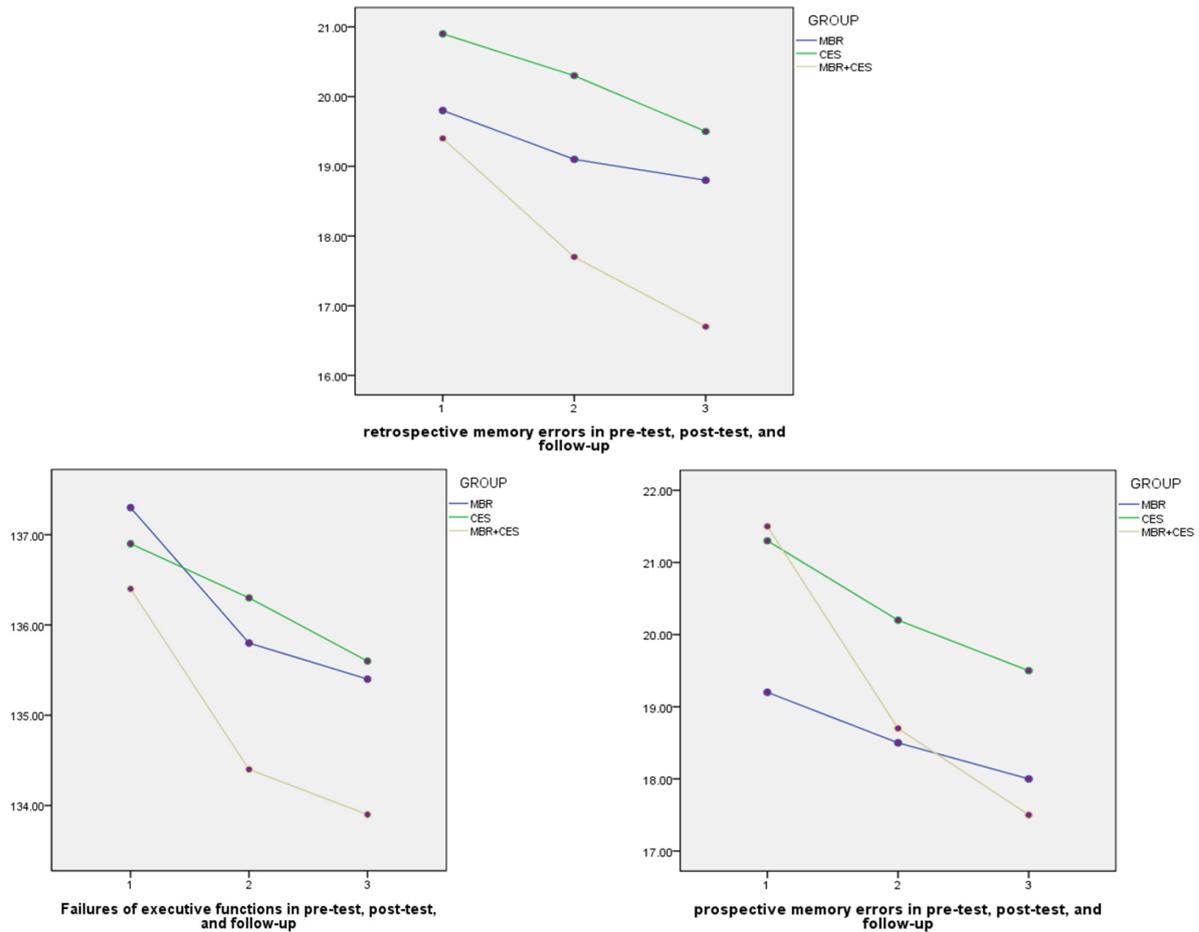


Figure 1. Triple Charts: From right to left, for executive functions, prospective memory, and retrospective memory in the groups, respectively

errors one month after the end of the interventions were less than the end of the interventions.

Discussion and Conclusion

The results of the study indicated the positive effect of the interventions used in reducing prospective and retrospective memory errors and were more in favor of MBR+CES combined therapy. But there was a tendency to decrease the mean of executive function failures, prospective, and retrospective memory errors in all three groups. Since MBR and CES have not been used for diabetes, it is not possible to compare the findings of the study with previous studies. However, the research findings that like MBR have taught mindfulness, breath control and breathing awareness to the learners are more or less in line with the findings of the present study which show that MBR intervention affects frontal cortex functions. Javanmard and Goli

(2018) designed research to show the effect of body function (mindfulness technics) on a brain product (Negative Emotions). The findings of their research showed that mindfulness-based stress reduction intervention is effective and useful as a supplement in addition to medications for decreasing negative emotions in patients with gastrointestinal disorders. Also, Herrero et al. (2018) who observed more severe respiration-locked oscillations in the amygdala during faster voluntary breathing than normal breathing, and according to their findings, breathing can act as a hierarchical organizing principle for neuronal oscillations throughout the brain and the partial mechanisms of how cognitive factors affect automatic neural processes during interceptive attention. Herrero et al. (2018) explain that voluntary breathing regulation, often used in cognitive-behavioral therapy and yoga/meditation techniques, when the subject is asked to breathe

faster, the rate and power of the respiration-locked oscillations increases and follow high-frequency breathing, particularly in the premotor, caudal-medial frontal, orbitofrontal, and motor cortex, insula, superior temporal gyrus, and amygdala. Zelano et al. (2016) also suggest that in humans, breathing not only leads to higher frequency rhythms in the hippocampus but also the stage of respiratory-related oscillations affects memory retrieval. The study of Jiang et al. (2017) also confirms the coherence associated with respiration in the olfactory bulb and hippocampus.

The structural changes in the brain are not studied in the present study, but it seems that continuous MBR training, especially when combined with CES, may also bring about structural changes in the brain along with functional changes because, according to the researches, mindfulness-based therapies cause structural and functional changes in the brain. In the study of Zimmerman et al. (2019), for example, evidence of changes in brain connectivity was found during the MBCT intervention in the default mode network (DMN) and amygdala. Also, Shojaei, Shamsipour Dehkordi, and Mootabadi (2019) found out choosing active lifestyle is recommended to fixed and rotating hospital employees in order to avoid reduction of quality of working life and memory self-efficacy. Interestingly, in both DMN and CON, the highest contrast was observed in connectivity at the follow-up session. In the DMN, a significant decrease in connectivity with the left calcarine sulcus and the right thalamus was observed from pre-intervention to follow-up session. Significantly, most significant changes in DMN connectivity occurred in contrast in the follow-up session. According to the results, Zimmerman et al. (2019) claim that the brain probably continues to adapt and adjust even after the intervention. Similar to the results of Zimmerman et al. (2019), it appears that, in the present study, structural and functional changes in the brain continued until the follow-up (one month) phase because the mean of prospective memory errors in the follow-up phase was also lower than in the post-test phase. In the study of

Yang et al. (2019), neuroimaging evidence also shows that mindfulness meditation skills are related to the different structural and functional configuration of the default mode network (DMN), salience network, and executive network. In this longitudinal study, amplitude of low-frequency fluctuations (ALFF) and structural changes following 40 days of short mindfulness-based meditation training and their relationship with the mood effects of practices were examined. The results emphasized the parietal cortex with a relative increase in cortical thickness in the left precuneus, which showed a significant decrease in ALFF. Other findings were related to the upper left parietal cortex and bilateral inferior parietal lobe (IPL), where increased cortical thickness in the left inferior temporal gyrus was associated with a decrease in the Spielberger State-Trait Anxiety Inventory (STAI) score after 40 days (Yang et al. 2019). In the present study, although MBR trainings were provided in 10 sessions, breathing awareness and mindfulness were associated with active relaxation practices, and the third group also had 10 sessions of CES, that CES itself causes structural and functional changes in the brain, it is not unlikely that due to the synergy of MBR and CES, functional changes have been associated with structural changes. As mentioned, evidence has also confirmed structural and functional changes in the brain following electrical stimulation of the brain. According to Ellsworth (2012), for example, the studies indicated that CES induces a mild stimulation in the hypothalamic region, leading to a balance in neurotransmitter activity. Some studies have also shown exciting improvements in memory and IQ scores suggesting that neural modulation can affect patients' cognitive performance. The CES technique increases the production of serotonin, gamma amino butyric acid (GABA) and endorphins. These neurochemical changes explain any positive effects that CES may experience (Ellsworth, 2012). Cranial stimulation also causes changes in biochemical components in blood and cerebrospinal fluid (Philip, 2017). Kennerly (2006) also claims that the use of low-level current in the

head can have profound cognitive, emotional, and motor effects. Concerning the insignificance of the reduction of executive function failure due to interventions, it seems that the instrument of measuring executive functions may measure the components of executive actions that could not be changed in 10 intervention sessions. Because the tool used in the study, the Barkley Deficits in Executive Functioning Scale, measures 5 executive functions of time management, self-management/problem solving, self-restraint, self-motivations, self-regulation of emotion, and the interventions of the study do not seem to have the capacity to change the five mentioned actions. However, in the present study, the overall score obtained from this tool was considered, and a tendency to decrease in the overall score of executive functioning deficits was observed. Parts of this reduction may be related to improvements in actions such as self-control, and self-regulation of emotion, and partly to improved memory performance. As Barkley (2006) suggests, memory action, as one of the essential and important actions of executive function, is essential to facilitate and properly perform the activity of other components of executive action, and its proper functioning provides sustained focus or attention, reflection on stimuli, and inhibition of irrelevant impulses to the situation. Therefore, it is suggested that future researches use other tools such as the Wisconsin Card Sorting Test to study executive functions. In this study, because diabetic patients met each other in the waiting room and in between sessions, using this tool was impossible because of the likelihood of learning how to sort cards and discovering the patterns. Overall, less attention has been paid to the effects of diabetes on cognitive function, whereas cognitive deficits are generally observed in diabetic patients (Wu et al., 2017; Exalto, Whitmer, Kappele & Biessels, 2012; Pearce, Noakes, Wilson & Clifton, 2012). Also, as noted in the beginning of this article, type 2 diabetes occurs more frequently in adults and in older adults, so the likelihood of cognitive aging associated with neuro-cognitive impairments in diabetes is high, and numerous studies have shown that working

memory is most vulnerable to the effects of normal and abnormal aging (Baddeley, 1986, and Glisky, 2007, as cited in Groome & Eysenck, 2019). Therefore, cognitive rehabilitation can be important for repairing working memory in diabetic and elderly patients. Positive effects of cognitive rehabilitation on reducing working memory and daily memory problems in MS patients have been shown in the study of Mousavi, Zare, Etemadifar, and Neshat Doost (2018b). They reported that even though cognitive rehabilitation has short-term effects, there are still positive changes in patients' self-assessment of reduced daily memory problems after memory rehabilitation. On the other hand, neuroimaging studies indicate an increase in the activity of the dorsolateral prefrontal cortex (PFC) of individuals involved in those cognitive tasks that require dynamic and flexible attention control, which are related to the functions of the central executive unit of working memory. Thus, it seems that this part of the prefrontal cortex activates the neural basis for executive control in working memory, the lateral ventricle. In contrast, the data retention element activates the lateral ventricle of working memory tasks. Studies have shown that when tasks require executive control, older participants exhibit higher levels of dorsolateral PFC activity than younger participants, and this case seems to reflect a decline in neural output in the area that requires higher levels of activation to achieve executive control (Hedden, 2007, as cited in Groome & Eysenck, 2019). In this regard, studies such as Hsu, Juan, and Tseng (2016) also suggest that anodic stimulation of the dorsolateral prefrontal cortex (DLPFC) increases the number of correct responses to working memory activity and anodic stimulation of the left DLPFC also improves the working memory performance (Zaehle, Sandmann, Thorne, Jancke & Herrmann, 2011) and reduces reaction time (Mulquiney, Hoy, Daskalakis & Fitzgerald, 2011), while no increase or decrease was observed in memory function after cathodic stimulation in the same brain region (Ohn, Park, Yoo, Ko, Choi, Kim, 2008; Zaehle et al., 2011). In Wu et al.'s (2014) study, the accelerating effect of

anodic tDCS on DLPFC is observed in memory span. Therefore, it is suggested that the future researches will use anodic stimulation protocols on DLPFC along with MBR exercises and cognitive rehabilitation techniques for diabetic patients and compare its results with the present study, in order to select more effective treatment for cognitive rehabilitation of diabetic patients and make better and more accurate decisions. It should be noted in previous studies that the authors of this article have performed on diabetic patients. Although computer-aided cognitive rehabilitation practices have been shown to affect memory, attention, and perception (Aghayousefi, Zare, Mohammadi Garegozlo, 2017; Alipoor, Mohammadi Garegozlo, 2019), they were not effective on executive functions (Alipoor, Mohammadi Garegozlo, 2019). Therefore, Javanmard and Mohammadi Garegozlo conducted a study in 2019, in which cognitive rehabilitation practices for working memory were presented simultaneously with anodic tDCS on the left DLPFC, and a significant increase was observed in both working memory and executive functions (according to the results of the Wisconsin Card Sorting Test). Hence, as discussed above, it is recommended that future researches use MBR and CES as complementary therapies along with cognitive rehabilitation techniques in order to improve memory and executive functions of diabetic patients.

Another suggestion is that, as studies suggest, memory error and the ability to recall prescriptions and treatment regimens recommended by a physician are associated with following treatment and affects it (Zahednejad et al., 2012), and the people's ability to remember other things about self-protection or other-protection (e.g., driving, turning off the gas, and child care) is very sensitive and important, and patients' cognitive dysfunction can affect their ability to complete their functional activities (Nair, Ferguson, Stark & Lincoln, 2012), in the unlikely events of a memory repair, it is recommended to use methods such as short notes for quick reminder, lecture notes file, cell phone for alert and reminder, phone book, Filofax, medicine

reminder alerts, notebooks for review of past events, planning device to determine appointments and tasks to be done and addresses, the notebook phone message to take notes of phone calls that help people with memory problems at the Oliver Zangwille Center (Wilson, 2015).

Concerning the limitations of the study, we faced limitations such as the inability to study structural changes in patients' brains due to high costs, as well as the inability to follow up more for treatment continuity due to the lack of time and some administrative difficulties. Therefore, it is suggested that in the future researches, brain structural changes be studied before and after the interventions in order to obtain information on changes in neuronal modulation following each of therapeutic techniques and following the synergy of techniques. According to the persistent effect and observed changes following mindfulness practices and breathing control, especially cranial stimulation CES, which most users report long-term improvement after two to three weeks of using CES (Ellsworth, 2012), it is recommended that two- and three-month follow up is performed after intervention completion in order to more precisely specify the efficacy and sustainability of the treatment.

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