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The Effectiveness of Transcranial Direct Current Stimulation (tDCS) and Omega-3 on Food Craving, Executive Functions, Weight, and Depressive Symptoms in Patients with Depression and Overweight: A Randomized Controlled Trial

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Abstract

Objective: The most important hypothesis of this research was based on the fact that the mechanism of the effect of omega-3 on depression and obesity is formed through its accumulation in the dorsolateral prefrontal cortex (DLPFC), especially in women. Accordingly, we investigated the omega-3 intake and the concurrent stimulation of the DLPFC by tDCS and hypothesized that the synergy of these two treatments can increase the obtained effect size in patients with depression and overweight.
Method: This research was a double-blind randomized controlled trial (RCT) with a factorial design consisting of four treatment and control groups. The participants were females with depression and overweight on an outpatient basis. They received 5 ml/day omega-3 syrup (545 mg DHA, 620 mg EPA) or placebo adjunct with 12 sessions sham/tDCS stimulation administered for 3 weeks with anode-left/cathode-right protocol in the prefrontal cortex (1.5 mA, 15 minutes' stimulation / 15-20 minutes' rest intervals/one visit per week, 4 stimulations per visit).
Results: tDCS or omega-3 alone did not significantly improve the executive functions, depression, food cravings, and weight in the experimental groups compared to the control group ($P > 0.05$). However, tDCS adjunct with the omega-3 had a significant and positive effect on improving weight change ($P = 0.011$; $df = 1$; $F = 1.27$; $Eta = 0.108$) with a power of 0.73 compared to the control group. Furthermore, their interaction led to an improving trend in executive functions and a decreasing trend in food cravings which are clinically important.
Conclusion: tDCS could strengthen the omega-3 mechanisms of effect through stimulating its accumulation site in the brain (i.e., the DLPFC) and the synergistic effects of these two treatments result in weight control as well as an improvement trend in the executive functions and food craving in women.

Key words: *Depression; Executive Function; Craving; Omega-3; Transcranial Direct Current Stimulation*

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Depression is a common global mental health problem. The literature shows that 3.8% of the world's population suffers from this illness, which means almost 280 million people around the world may experience the symptoms of depression (1-3). Also, studies show that depression is related to personal, social, occupational, educational, and economic problems (4). Furthermore, studies have investigated that depression is associated with some chronic conditions including obesity and overweight (5, 6).

Obesity is also a global health issue that affects more than 650 million adults around the world and is correlated with a high risk of developing many other health problems (7). In fact, obesity and depression have common symptoms such as sleeping and eating (food) disorders as well as changes in appetite and food cravings (8). The etiology of obesity is multifactorial involving biological, behavioral, and environmental factors. Hedonic appetite, which is correlated with the rewarding system, is a cause of overeating (9). On the other hand, investigations have shown that food craving is related to deregulation in serotonergic system and depressive symptoms (10).

Improvement of the executive functioning, which originates from the prefrontal cortex (PFC), could lead to better control of food craving by inhibiting impulsive signals. The subjects with obesity may show impulsive behaviors to food cues as a result of changed PFC activity (11). It is suggested that a decrease in the right dorsolateral PFC (DLPFC) activities may lead to obesogenic behaviors through poor appetite control (12). In fact, irregularity in DLPFC is connected to higher impulsive actions (13) and reactions that usually cause overeating. Intensifying the DLPFC activity may enhance the ability to control food craving, proposing an innovative method in the field of obesity treatment (14).

In the past years, applying neurostimulation therapy, especially transcranial direct current stimulation (tDCS) has achieved a universal interest in the treatment of neurological conditions (15, 16). Through tDCS, a low-intensity current of often less than or equal to 2 milliamps (mA) is applied at the scalp level (17). However, it is important to note that only a fraction of this current, estimated in the order of tens of microamperes, actually reaches the neural system, typically targeting areas like the DLPFC (18, 19). Therefore, tDCS is not considered an invasive procedure (20). It has also been indicated that the DLPFC stimulation by tDCS will decrease hedonic appetite and food carving, leading to less food consumption, and it happens by weakening the reward response (21, 22). In spite of applying very similar tDCS parameters, some incompatible findings are observed. Some studies have shown that this method might be effective in treating eating-related problems such as obesity and food cravings (23, 24). In particular, studies aiming to decrease food craving and food consumption have targeted the DLPFC with 2-mA current and a left cathode/right anode protocol in one session. Trials performed with a similar protocol on different populations reported a decrease in food and calorie intake (25). Another study stated that when stimulation was conducted with 1 mA instead of 2 mA, food cravings did not change (26). Furthermore, those studies that employed a right cathode/left anode protocol over the DLPFC indicated uncertain outcomes in food carving and eating (27). The findings of Mostafavi *et al*. revealed a substantial effect of the neuromodulation of the DLPFC by tDCS in energy intakes and food cravings. These results recommend applying multi-session bilateral stimulation of the DLPFC with a 2-mA power to reduce food carving (28). Furthermore, Beaumont *et al*. reported that applying tDCS is effective in treating patients with food cravings (29). These controversial findings indicate the need for more clinical studies in this field.

Furthermore, another application of tDCS that recently has gained popularity is in the treatment of depression by enhancing or suppressing the excitability of the DLPFC (30). While some trials have demonstrated the clinical efficacy of tDCS in treating depression, a meta-analysis synthesizing results from multiple studies reported a response rate of approximately 20%, indicating that its efficacy in treating depression may be considered moderate (31).

However, in order to make tDCS more effective, it is recommended to combine it with other therapies (32). Despite the side effects of antidepressants, it is considered crucial to find a safe treatment regimen that targets depression and at the same time improves executive functions and obesity effectively (33). Omega-3 fatty acids are dominantly accumulated in the brain. The association between omega-3 deficiency (in plasma and cell membrane) and depression is well-established. The neuronal anti-depressive mechanisms induced by omega-3 fatty acids include neurotransmitters modulation, anti-inflammatory effects, structural role, and plasticity of neuronal membrane mainly in synapses (34). Augmentation of omega-3 to the first-line antidepressants is an emerging treatment regimen for depression (35). It possibly has positive effects on the prevention and treatment of depressive symptoms (36). Several reviews have demonstrated the positive effect of omega-3 on depressive symptoms (37). The severity of depression symptoms and EPA to DHA ratio were important factors in determining the efficacy or lack of efficacy of omega-3 (38, 39).

In addition, the omega-3 supplement (fish liver oil) is a popular medicine with no specific side effects. It can reduce obesity by increasing fat oxidation which causes a beneficial effect on both glucose and fat metabolism (40). It also affects membrane composition and ions permeability. Based on the findings of Mostafavi *et al*., the consumption of omega-3 capsules as a secure over-the-counter supplement was effective in decreasing

symptoms of depression in patients with both depression and obesity. Moreover, these patients receiving omega-3 capsules were significantly more successful in reducing their body weight compared to those receiving placebo (41). However, there are conflicting outcomes regarding the effect of omega-3s on appetite suppression, followed by body fat reduction, which requires further investigations. In addition, nutritionists believe that omega-3 fatty acids can improve some executive functions and have anti-inflammatory effects (42). Although existing literature does not exactly specify the mechanism of the omega-3 supplement's effect on executive dysfunction in depressed adults, there are hypotheses that its consumption may be effective (43).

Considering the significant interrelationship among obesity, depression, and executive functions, particularly in the female population, and their mutual impact on each other's prognosis, it becomes evident that none of them can be pinpointed as the sole cause of the other. This highlights the necessity for more comprehensive clinical research in this area. Since existing studies are one-dimensional, no study has yet simultaneously examined the effect of the electrical stimulation of the brain or omega-3 supplement and their interactions on food cravings, body weight, depressive symptoms, and executive functions in women with depression and overweight.

The most important and main hypothesis of this research was based on the fact that the mechanism of effect of omega-3 on the symptoms of depression as well as obesity is formed through its accumulation in the DLPFC, especially in women. Accordingly, we investigated the consumption of omega-3 and the concurrent stimulation of the DLPFC by tDCS, hypothesizing that the synergy of these two treatments can increase the obtained effect size in these patients. Hence, we aimed to perform a double-blind randomized controlled trial (RCT) using a factorial design and examine the effects of tDCS, omega-3, and their interactions on food cravings, executive functions, depressive symptoms, and anthropometric indices of women with depression and overweight/obesity in comparison with the control group.

Materials and Methods

Study Design

This research was a double-blind placebo-controlled randomized trial with a factorial design consisting of three treatment groups and a control group.

Participants

The medication-free women aged 18-60 years who were referred to a private clinic on an outpatient basis were invited to participate in the research and assessed for eligibility. The symptoms of depression were evaluated through a psychiatrist via the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria. Then, patients' accurate height and weight were measured, and the Body Mass Index (BMI) was assessed through Quetelet's index formula. Those diagnosed with mild and moderate depression, with a BMI $\geq$ 25, were enrolled.

Inclusion/Exclusion Criteria

Inclusion criteria: Women with mild to moderate depression according to the DSM-5 criteria, Beck Depression Inventory scores above 14, being categorized as obese or overweight (BMI $\geq$ 25), and aged between 18-60 years old. Non-inclusion criteria: Unwillingness and not consenting to participate in the study, being pregnant or breastfeeding, other major psychiatric illnesses such as bipolar depression, schizophrenia, neurological diseases such as epilepsy, history of major head trauma and neurofeedback in the last two months, past electroconvulsive therapy, alcohol or drug dependency, learning disabilities, and uncorrected visual problems. Exclusion criteria: Canceling the participation in the study for any reason (cancellation due to a side effect was recorded), not compliance with the study protocol.

Study Procedure

At the beginning of research, the included participants who had signed informed consent forms were allocated randomly to one of four groups without any interference by the researchers. Also, the groups had been hidden from both researchers and patients (double-blinded) by coding and placebo or sham. The trial groups were as follows:

1st group: (tDCS + omega3) representative of the interaction of tDCS and omega-3

2nd group: (sham + placebo) as the control group for comparison

3rd group: (sham + omega3) representative of the omega-3 effect

4th group: (tDCS + placebo) representative of the tDCS effect

The tDCS device was blinded for the real stimulation and sham. The device protocols were coded according to protocols 1 & 2, and the researcher was unaware of those protocols.

The interventions dosage and protocol were as follows: mercury-free omega-3 syrup in a dosage of 5 ml per day (German euro vital; 545 mg DHA, 620 mg EPA) or placebo (soybean oil) in a dosage of 5 ml per day. Real and sham tDCS were applied through the tDCS device (NEUROSTIM2corp.). A constant current of 1.5 mA, with a 30 s fade in/out, was applied through two 5 cm * 7 cm surface sponge electrodes fixed on the head with suitable straps. Before stimulation, the electrodes were sufficiently soaked in sterile saline solution (0.9% sodium chloride). We used the international 10-20 system to place the electrodes on the head. Accordingly, the cathode and anode were located on F4 (the right DLPFC) and F3 (the left DLPFC), respectively. The sham stimulation was applied in such a way that the device automatically turned off after 30 seconds without notification to the subjects. Twelve sessions of tDCS

stimulation or sham were delivered to patients during three weeks as follows: one visit once a week, consisting of 4 stimulation sessions each time with an intensity of 1.5 mA and 15 minutes duration/15 to 20 minutes rest. Moreover, to reduce the effect of different diets on the study outcomes, all participants received a unified-500 kcal diet from their usual intake by a registered dietitian. The researchers also monitored the participants' adherence to the study protocol, including supplement consumption and diet, via telephone calls, face-to-face visits, and continuous evaluation of the consumption of the syrup by every single time checking the remained syrup in its bottle.

During the 1st visit (1st day) and before starting the brain stimulation, the aim of the research, study protocols, and cooperation modality were explained to the participants in advance, and the consent letters were voluntarily signed by the participants. Then demographic information followed by "Beck Depression Inventory (BDI) II, Simple Appetite Questionnaire and Food Craving Questionnaire, Stroop test software, and Wisconsin card classification software" were completed as a pre-test by the participants. Their heights were carefully measured by an inelastic meter, and their weight, BMI, and body composition were accurately measured by a body analyzer. Furthermore, the participants received electrical stimulation/sham 4 times and received their omega-3 syrup/ placebo and its consumption instruction.

During the 2nd and 3rd visits (days 7 and 14), the subjects received electrical stimulation four times, and their weight and body composition were measured. Additionally, the participants' adherence to their diets and accurate consumption of supplements were monitored; finally, they received the necessary feedbacks.

As the post-test, in the 4th visit (day 21), the participants completed the Beck Depression Inventory II, Simple Appetite Questionnaire, Food craving Questionnaire, Stroop test software, Wisconsin card classification software, and their body composition were recorded. In addition, the researcher-made questionnaire on the side effects of brain electrical stimulation was also completed by the participants. On this day, all interventions were stopped.

At the follow-up visit (day 28), which was the stage of following up and measuring the durability of the treatment effect, all measurements were repeated. Evaluations were performed in three stages as follows: days 0, 21, and 28.

Study Tools

Beck Depression Inventory-II

The BDI-II is the most utilized tool to evaluate the existence and intensity of depressive symptoms. This tool is a 21-item index of self-reported symptoms of depression in subjects aged 13 years and older across different clinical and non-clinical populations. Each question of the BDI-II is scored in the range of 0 to 3, 0 for the absence of a specific sign and 3 for the maximum degree of that sign. A score ranging from 0 to 13 confirms no or minimal depression, while a score ranging from 14 to 19 indicates mild depression. A score between the range of 20 to 28 confirms a moderate level of depression, and a score ranging from 29 to 63 indicates severe depression (44). Ghasemzadeh and colleagues showed that the content validity of this inventory measured by the Cronbach's alpha method is 0.87 and its test-retest reliability is 0.74 (45).

Simplified Nutritional Appetite Questionnaire (SNAQ)

The SNAQ was constructed and introduced by the Nutrition Strategies Council to assess appetite. The reliability and validity of its original form have been confirmed in a publication by Wilson *et al*. (46) This questionnaire is one of the most practical tools in the field of measuring appetite in the world. The reliability and validity of the Persian version of this questionnaire were examined by Mohammadi *et al*., in 2018. The content validity of the test was confirmed through Cronbach's alpha coefficient of 0.7. The test-retest reliability of this tool has also been confirmed with a correlation coefficient of 0.85 (47).

Food Craving Questionnaire-Trait Reduced (FCQ-Tr)

The FCQ-Tr is widely applied to evaluate craving. This tool estimates the psychometric properties of food craving in general rather than estimating craving for specific foods. In addition, the questionnaire considers various aspects of food craving, including behavioral, physiological, and cognitive dimensions. The FCQ was first developed by Cepeda-Benito and colleagues. The original questionnaire consists of 39 items. Later, a shorter form of this questionnaire entitled the FCQ-Trait, reduced (FCQ-Tr), was presented with 15 questions. The Persian version of the FCQ-Tr questionnaire demonstrated acceptable content validity and its Cronbach's alpha coefficient was equal to 0.90. In addition, the test-retest reliability of this tool was approved with a correlation coefficient of 0.92 (48). In this trial, the reduced version of this questionnaire was used to measure the food craving of volunteers and their total scores were recorded.

Stroop Word and Color Test

The Stroop tool was built by Ridley Stroop for assessing selective attention, response inhibition, cognitive variability, and cognitive flexibility by applying visual processing. Selective attention is the ability to process related data while eliminating irrelevant or incorrect data. In the present study, the computer type of this test was used, which consists of the following three steps:

Step-1 Preliminary: In this step, the client was requested to answer by pushing a key that matches the color of the circle she observes on the screen (the circle was shown in four colors including blue, red, green, and yellow). The purpose of this step is only to exercise and practice colors and place of the keys on the keyboard, and the final result is not recorded. For each answer, the

feedback on the true or false answers is demonstrated on the screen.

Step-2 Trial: In this step, the method explained in the next step is exactly performed. The aim of this stage is to practice and get familiar with the way of responding and the placement of keys on the page, and hence the results are not recorded. For each answer, the feedback on the true and false answers is demonstrated on the screen. (Note: depending on the test conditions, the above steps could be optional and the researcher could uncheck them).

Step-3 Performing the Stroop test: Here, 48 congruent colored words and 48 incongruent colored words with blue, red, green, and yellow colors are presented to individuals. Congruent words are those words in which the color of the word and its meaning is the same (for instance, the word green, which is displayed by the green color). On the other hand, incongruent words mean that the color of the word does not match the meaning of the word (for instance, the word is considered blue but comes in yellow). Totally, 96 incongruent and congruent words are displayed randomly and one after another. The client was only supposed to identify the appearance of the words, regardless of the meaning of the words. Two seconds was the time that the stimulus was displayed on the screen. In this study, the *interference time* variable was used to measure clients' response inhibition changes. The *interference time* variable is calculated by subtracting the time of counting incongruent correct responses from the number of congruent correct responses. In the analysis of pre-test and post-test results, if the result of this subtraction (interference time) is positive, it means less change and improvement in response inhibition. The closer the number is to zero and negative, the faster the reaction time, and the better the response inhibition in the participants. The test-retest reliability coefficient of the Stroop test was 0.88 (49).

Wisconsin Card Sorting Test (WCST)

The WCST was introduced by Grant and Berg. In this tool, the patient is presented with a set of 64 cards. On these cards there are one to four shapes in the form of triangle, star, plus, and circle which come in four colors: blue, red, green, and yellow. Of course, no two cards are alike. Four cards, including two green stars, a red triangle, three yellow plus and four blue circles, are utilized as the principal cards. The client is supposed to put the next cards under the principal cards based on the color, the shapes or number according to the feedback received by the computer. After each answer, the client receives feedback showing whether their answer was correct or incorrect. Indeed, individuals are asked whether the replacement is right or wrong. The category pattern for the four principal cards is based on color, shape, and number, and this task is performed twice.

When the client has given enough true responses in a row, the desired pattern changes, but the client is not aware of the pattern change and should discover it herself. The two major indicators of the client's performance are "*number of categories completed (achieved)*" and "*number of perseverative errors*". In this study, the index of perseverative errors has been reported and it means that the person repeatedly persists in choosing the incorrect category. The unit of this index is numeric. We used the computerized software version of the WCST. Internal consistency for this version was confirmed through Cronbach's alpha: 0.74 for the count of perseverative errors, and 0.73 for the count of categories completed. Furthermore, split-half coefficient was 0.87 for the count of perseverative errors and 0.83 for the count of categories completed (50).

Measuring Height, Weight and Body Composition

The client's height was measured with an inelastic meter, with accuracy to the nearest centimeter while she was standing straight beside the wall. Weight and body composition measurements of clients were performed by BF 511 body composition analyzer device, which is one of the products of the Omron brand made in Vietnam under the license of Japan. In addition to accurate weight and body mass index, this device gives a comprehensive measurement of the visceral fat, total fat percentage, and skeletal muscle mass.

Side Effect Questions

There was no any standard questionnaire for this purpose. Hence, we gathered a frequently reported side effect checklist based on previous tDCS articles. The researcher asked the clients about the common complications experienced during the study. The checklist included headache, itching, burning, vertigo, anxiety, stress, forgetting, tingling, lethargy, discomfort, insomnia, and irritation.

Statistical Methods

To assess the hypotheses of the study, the data were collected and analyzed by relevant statistical methods. First, descriptive statistics like means and standard deviations were measured, then assumptions were checked and finally inferential statistics were used. In the initial checking, the baseline variables and known covariate were statistically distributed equally between the groups; hence no uncontrolled known covariate were left. The normality of distribution and equality of variances and independency of each observation were assumed. Thus, we employed Analysis of Variance (ANOVA). Scheffe's post hoc test was used to perform pair wise comparisons. Furthermore, we assessed the tDCS effect (the groups receiving tDCS compared to the groups not receiving tDCS), omega-3 effect (the groups receiving omega-3 compared to the groups not receiving omega-3) and their interactions on outcome variables using Multivariate Analysis of Variance (MANOVA). Before performing MANOVA, we checked some assumptions which include examining the outlier values, evaluating the normality of the dependent variables (by histogram and Kolmogorov-Smirnov tests), assessing the linear relationship between the dependent variables by scatter diagram, examining the homogeneity of variance

(by Levins test) and the homogeneity of the regression slope. Furthermore, we used the Chi-square test to assess the relationship between nominal variables of side effects and study groups. We used the SPSS 19 software (SPSS Inc., Chicago, Ill., USA) to analyze the data.

Ethics Considerations

The research protocol was certified by the "ethics in the research committee" of Tehran University of Medical Sciences (Ethics code: IR.TUMS.VCR.REC.1398.564). Before enrolling the clients, we provided them with a description of the objectives and protocol of the research, and the possible benefits and side effects of the intervention, and in case of their interest, the consent was obtained, consciously and freely. Our study was approved and registered in the IRCT Clinical Trials Registration Center of Iran with ID 50663.

Results

In the end, 64 clients accomplished the trial and entered into the analyses. Figure 1 demonstrates the flow diagram of the research. At the baseline, there were not any significant differences between groups regarding the background and main variables (Table 1). The study of the description of mean and standard deviation of dependent variables in the four time periods of the study group based on the ANOVA test indicates that there were significant differences between the groups regarding the body weight change during the study (Table 2). Scheffe's post hoc test for weight changes indicated that the significance results were related to the tDCS adjunct with omega-3 group compared to the sham and omega-3 group (P = 0.02).

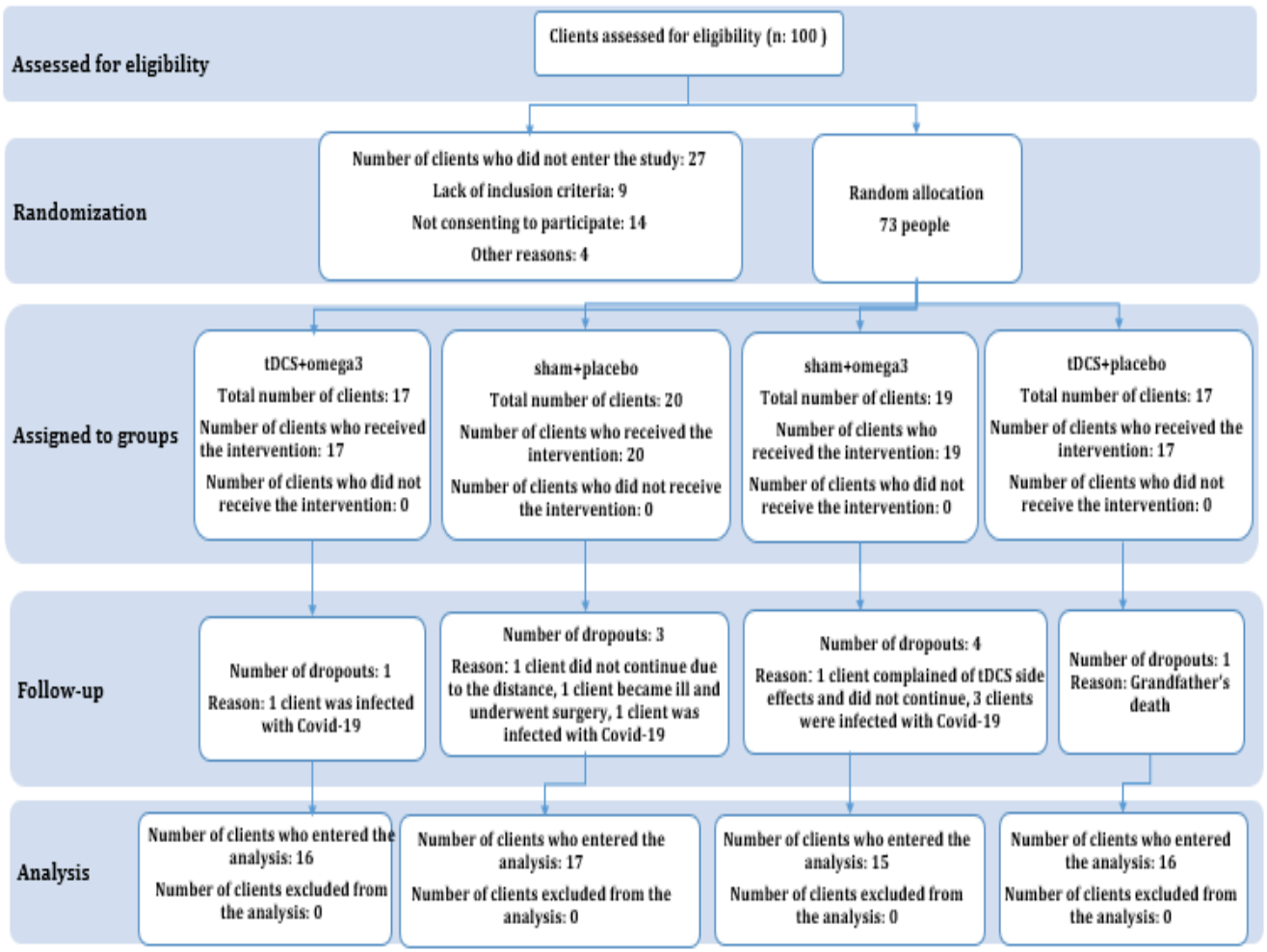

Figure 1. The Flow Diagram of the Clinical Trial on The Effectiveness of tDCS and Omega-3 in Patients with Depression and Overweight. The Diagram Showes the Number of Clients in Each Stage of Assessment, Randomization,Groups Asignment, Follow-up and Analysis

Table 1. Mean and Standard Deviation of Variables at the Beginning of the Study

Variable	GROUP 1 (Tdcs + omaga3)	GROUP 2 (sham + placebo)	GROUP 3 (sham + omega3)	GROUP 4 (tDCS + placebo)	df (between group)	F	Sig*
Age(year)	39 ± 8	40 ± 10	41 ± 12	37 ± 10	3	0.612	0.61
Depression rate (number)	26.63 ± 7.8	26.29 ± 10	25.13 ± 7	26.25 ± 9.64	3	0.085	0.97
Weight (kg)	81.84 ± 14.9	81.43 ± 12.11	81.34 ± 10	81.8 ± 16.6	3	0.005	0.99
Body mass index (weight in height squared in meters)	32.08 ± 5.82	30.78 ± 4.95	32.51 ± 4.82	31.13 ± 6.35	3	0.339	0.79
Food craving (number)	44.63 ± 16.62	45.53 ± 11.45	45.87 ± 16.42	45 ± 14.97	3	0.021	0.99
Appetite rate (number)	14.88 ± 3.22	14.94 ± 2.51	15.60 ± 3	15.56 ± 2.63	3	0.300.	0.82
Number of perseverative errors on the Wisconsin test	3.56 ± 2.66	4.53 ± 4	4.93 ± 4.62	3.19 ± 2.86	3	0.801	0.49
Number of categories completed in the Wisconsin test	4.56 ± 1.8	4 ± 1.1	4.4 ± 1.72	4.63 ± 1.67	3	0.421	0.73
Interference time in the Stroop test (milliseconds)	45 ± 43.46	71.41 ± 49.63	63.47 ± 38.25	83.56 ± 101.46	3	1.04	0.38

* P-values are based on ANOVA test

Table 2. Description of Mean and Standard Deviation of Dependent Variables in 4 Time Periods of the Study Using ANOVA Test

Dependent variables	Groups	Number of Clients	Mean ±Standard Deviation at the Beginning of the Study	Mean±Standard Deviation in the Third Week of the Study	Mean±Standard Deviation of Changes During the Study	p. value Changes	Number of Clients in the Follow-up	Mean±Standard Deviation in Follow-up	Mean±Standard Deviation of Follow-up Changes Compared to the Third Week	p. value Follow up
Depression	tDCS + Omega3	16	26.63 ± 7.78	20.31 ± 8.4	-6.31 ± 5.97	0.49	16	23.69 ± 11.11	3.38 ± 7.3	0.16
	Sham + Pelacebo	17	26.29 ± 9.94	17.53 ± 9.58	-8.76 ± 10.44		16	16.06 ± 10.12	-0.63 ± 7	
	Sham + Omega3	15	25.13 ± 7.05	19.73 ± 11.17	-5.4 ± 7.32		15	17.67 ± 8.17	-2.06 ± 8.7	
	tDCS + pelacebo	16	26.25 ± 9.64	21.56 ± 6.86	-4.69 ± 7.74		16	22.69 ± 7.01	1.13 ± 4.2	

Weight	tDCS+Omega3	16	81.84 ± 14.9	82.31 ± 13.71	-0.47 ± 1.07	0.01*	16	80.6 ± 14.23	-1.71 ± 0.9	0.45
	Sham+Pelacebo	17	81.43 ± 12.11	80.9 ± 12	-0.55 ± 0.7		16	80.29 ± 12.4	-0.61 ± 1.01	
	Sham+Omega3	15	81.34 ± 10.05	81.7 ± 9.8	0.36 ± 1.24		15	81.75 ± 10.16	0.05 ± 1.14	
	tDCS +pelacebo	16	81.81 ± 16.6	81.4 ± 16.4	-0.44 ± 0.1		16	81 ± 16.34	-0.24 ± 0.77	
Appetite	tDCS+Omega3	16	14.88 ± 3.22	12.69 ± 2.73	-2.19 ± 2.51	0.79	16	13.19 ± 2.64	0.5	0.25
	Sham+Pelacebo	17	14.94 ± 2.51	13.53 ± 2.94	-1.41 ± 3.1		16	13.06 ± 2.52	-0.5	
	Sham+Omega3	15	15.60 ± 2.97	14.07 ± 3.26	-1.53 ± 3.04		15	13.60 ± 3.62	-0.46	
	tDCS +pelacebo	16	15.56 ± 2.63	14.25 ± 2.6	-1.31 ± 2.15		16	13.63 ± 2.7	-0.63	
Food craving	tDCS+Omega3	16	44.63± 16.63	33.06 ± 7.29	-11.56 ± 13.26	0.86	16	30.88 ± 6.9	-2.19 ± 5.36	0.79
	Sham+Pelacebo	17	45.53 ± 11.45	34.59 ± 9.73	-10.94 ± 12.22		15	33.87 ± 13.04	-0.73 ± 6.25	
	Sham+Omega3	15	45.9 ± 16.42	35.93 ± 12.92	-9.93 ± 11.36		15	35.87 ± 12.6	-0.07 ± 6.73	
	tDCS +pelacebo	16	45 ± 15	37.19 ± 14.96	-7.81 ± 15.16		16	35.13 ± 13.8	-2.06 ± 9.06	
Number of perseverative errors on the Wisconsin test	tDCS+Omega3	16	3.56 ± 2.7	2.38 ± 2.39	-1.19 ± 2.43	0.72	10	4.70 ± 3.5	2.32 ± 2.45	0.19
	Sham+Pelacebo	17	4.53 ± 4	4.76 ± 5.9	0.24 ± 5.3		14	3.43 ± 4	-1.42 ± 3.64	
	Sham+Omega3	15	4.93 ± 4.6	4.8 ± 4.4	-0.13 ± 3.2		11	4.27 ± 6	-0.53 ± 3.8	
	tDCS +pelacebo	16	3.19 ± 2.86	2.56 ± 3.5	-0.62 ± 3.3		10	1.90 ± 2	-0.66 ± 2.4	
Interference time in the Stroop test	tDCS+Omega3	16	45 ± 43.5	72.19 ± 91.84	27.19 ± 94.47	0.35	9	27.33 ± 48.9	-44.86 ± 47.1	0.84
	Sham+Pelacebo	17	71.41 ± 49.63	67.88 ± 56.35	-3.53 ± 69.8		12	41.33 ± 51.01	-26.55 ± 67.45	
	Sham+Omega3	15	63.47 ± 38.25	47.27 ± 39.25	-16.20 ± 38.56		11	35.09 ± 26.61	- 12.18 ± 21.91	
	tDCS +pelacebo	16	83.56 ± 101.46	79.19 ± 70.41	-4.37 ± 62.36		10	72.70 ± 51.55	-6.49 ± 52.93	

***** Scheffe Post hoc test for weight changes indicates that the significancy was related to the tDSC + omega-3 group compared with Non tDCS+omega3 group (p= 0.02)

Groups receiving tDCS (tDCS effect) were compared with groups not receiving tDCS (non-tDCS effect), and participants' scores on depression, food craving, executive functions (simple Stroop and Wisconsin cards), and weight were included in this model as dependent variables using the MANOVA test. The outcomes of this analysis are presented in Table 3. The omega-3 receiving groups (omega-3 effect) were compared with non-omega-3 groups (non-omega-3 effect), and participants' scores on depression, food craving, executive functions (simple Stroop and Wisconsin cards), and weight were included in this model as dependent variables using the MANOVA test, which also indicates no significant differences between the groups (Table 4). However, the interaction effects of tDCS stimulation and non-stimulation with omega-3 consumption and non-consumption by the MANOVA test indicates that the tDCS adjunct with the omega-3 had a significant and positive effect on improving weight change ($P < 0.011$; df = 1; F = 1.27; Etta = 0.108) with a power of 0.73 (Table 5). However, the results showed that tDCS and omega-3 alone did not significantly improve the executive functions, depression, food craving, and weight in the experimental groups compared to the control group ($P > 0.05$).

Table 3. The tDCS Effect* in Comparison with the Non-tDCS Effect* on Dependent Variables Studied by MANOVA Test

Dependent variables (changes in the third week)	Mean (95% confidence interval) tDCS effect N = 32	Mean (95% confidence interval) non-tDCS effect N = 32	df	Average squares	F	sig	Squared Etta	Power
Depressive changes	-5.69 (-8.23 to -3.1)	-6.89 (-9.48 to -4.3)	1	22.142	0.422	0.519	0.007	0.098
Changes in food craving	-9.23 (-13.71 to -4.76)	-10.9 (-15.38 to -6.42)	1	42.914	0.273	0.603	0.005	0.081
Changes in appetite	-1.71 (-2.67 to -0.764)	-1.51 (-2.46 to -0.55)	1	0.696	0.097	0.757	0.002	0.061
Changes in weight	-0.59 (-0.94 to -0.24)	-0.12 (-0.47 to -0.24)	1	3.428	3.54	0.065	0.058	0.456
Changes in Stroop interference time	10.8 (-14.3 to 35.9)	-9.28 (-34.44 to 15.9)	1	6255.383	1.26	0.266	0.022	0.197
Changes in the number of perseverative errors on the Wisconsin test	-0.94 (-2.31 to 0.423)	0.09 (-1.28 to 1.45)	1	16.446	1.12	0.294	0.019	0.180

* tDCS effect: Groups receiving tDCS (tDCS+omega3 and tDCS+placebo), non-tDCS effect: groups not receiving tDCS (sham+placebo and sham+omega3)

Table 4. The Omega-3 Effect * Compared to the Non-Omega-3 Effect* on Dependent Variables Studied by MANOVA Test

Dependent Variables (Changes in the Third Week)	Mean ± Standard Veviation of Omega-3 Effect (n = 31)	Mean ± Standard Deviation of the Non-Omega-3 Effect (n = 33)	df	Average Squares	F	Sig	Squared Etta	Power
Depressive changes	-5.81 (-8.42 to -3.19)	-6.78 (-9.31 to -4.25)	1	15.081	0.287	0.594	0.005	0.082
Changes in food craving	-10.93 (-15.45 to 6.42)	-9.21 (-13.58 to -4.83)	1	47.507	0.302	0.585	0.005	0.084
Changes in appetite	-1.88 (-2.84 to -0.91)	-1.35 (-2.28 to -0.41)	1	4.38	0.611	0.438	0.011	0.120
Changes in weight	-0.22 (-0.57 to 0.14)	-0.49 (-0.83 to -0.14)	1	1.150	1.18	0.280	0.020	0.188
Changes in Stroop interference time	5.63 (-19.73 to 31)	-4.12 (-28.69 to 20.48)	1	1508.623	0.304	0.583	0.005	0.084

Changes in the number of perseverative errors on the Wisconsin test	-0.65 (-2.02 to 0.73)	-0.21 (-1.55 to 1.13)	1	3.045	0.208	0.650	0.004	0.073

* Omega-3 effect: Groups receiving omega-3 (tDCS+omega3 and sham+omega3), non-omega-3 effect: groups not receiving omega-3 (sham+placebo and tDCS+placebo)

Table 5. Interaction Effects of tDCS Stimulation and Non-Stimulation with Omega-3 Consumption and Non-Consumption in Dependent Variables Studied by MANOVA Test

Dependent variables (changes in the third week)	Average (with 95% Confidence)				df	Average squares	F	sig	Squared Etta	Power
	tDCS stimulation and omega-3 consumption	Non stimulation of tDCS and consumption of omega-3	tDCS Stimulation and non-consumption of omega-3	Non stimulation of tDCS and non-consumption of omega-3						
Depressive changes	-6.24 (-9.87 to -2.61)	-5.38 (-9.15 to -1.62)	-5.16 (-8.82 to -1.5)	-8.41 (-11.93 to -4.88)	1	66.699	1.27	0.264	0.022	0.198
Changes in food craving	-11.21 (-17.5 to -4.92)	-10.66 (-17.18 to -4.14)	-7.27 (-13.6 to -0.93)	-11.15 (-17.25 to -5.04)	1	78.339	0.498	0.483	0.009	0.107
Changes in appetite	-2.14 (-3.48 to -0.8)	-1.61 (-3 to -0.22)	-1.29 (-2.64 to 0.06)	-1.41 (-2.71 to -0.1)	1	1.659	0.231	0.632	0.004	0.076
Changes in weight	-0.77 (-1.27 to -0.28)	0.34 (-0.17 to 0.85)	-0.4 (-0.9 to 0.09)	-0.57 (-1.05 to -0.09)	1	6.650	1.27	0.011	0.108	0.731
Changes in Stroop interference time	27.13 (-8.16 to 62.42)	-15.86 (-52.48 to 20.76)	-5.52 (-41.01 to 30.04)	-2.7 (-36.1 to 31.6)	1	8351.089	1.68	0.200	0.029	0.248
Changes in the number of perseverative errors on the Wisconsin test	-1.2 (-3.12 to 0.72)	-0.09 (-2.1 to 1.9)	-0.68 (-2.62 to 1.25)	0.27 (-1.6 to 2.13)	1	0.105	0.007	0.933	0.000	0.051

The results of examining the mean of the interaction effects for appetite changes in the experimental groups are exhibited in Figure 2. It shows that the group exposed to both tDCS stimulation and omega-3 had the most decrease in appetite than the other groups. In spite of not observing a significant statistic difference between the groups, the findings are clinically important.

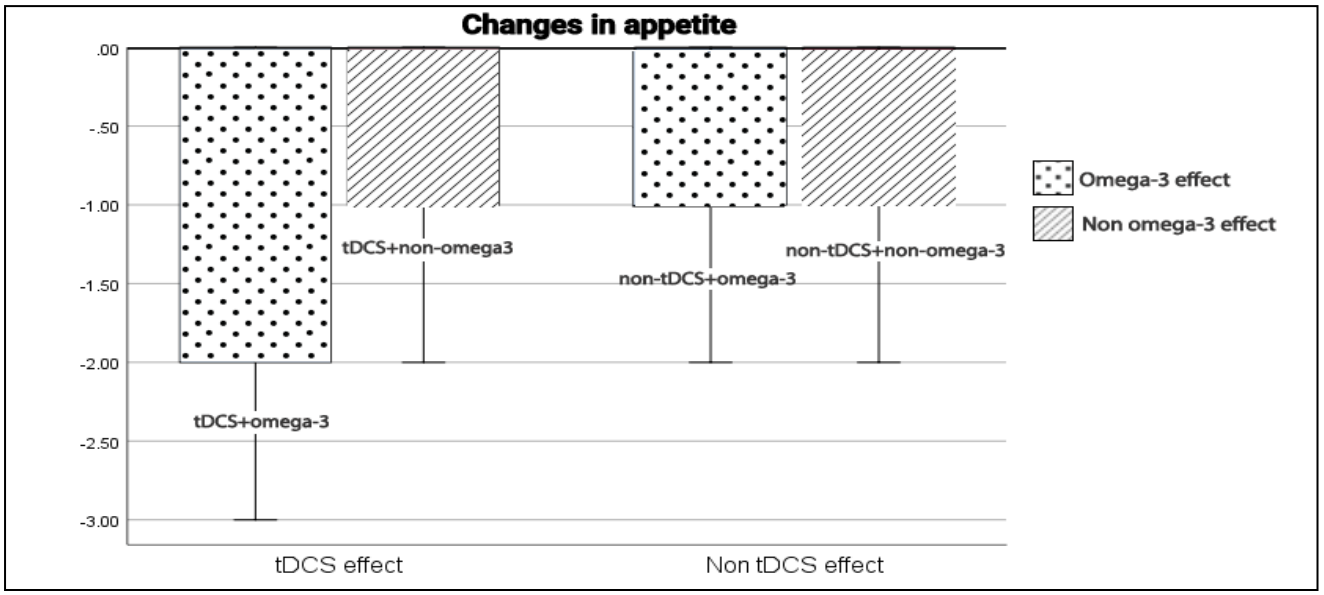

Figure 2. Interaction Effects of Stimulation/non-Stimulation of tDCS and Consumption/non-Consumption of Omega-3 Regarding the Appetite Changes During the Study. Error Bars: 95% Confidence Intervals

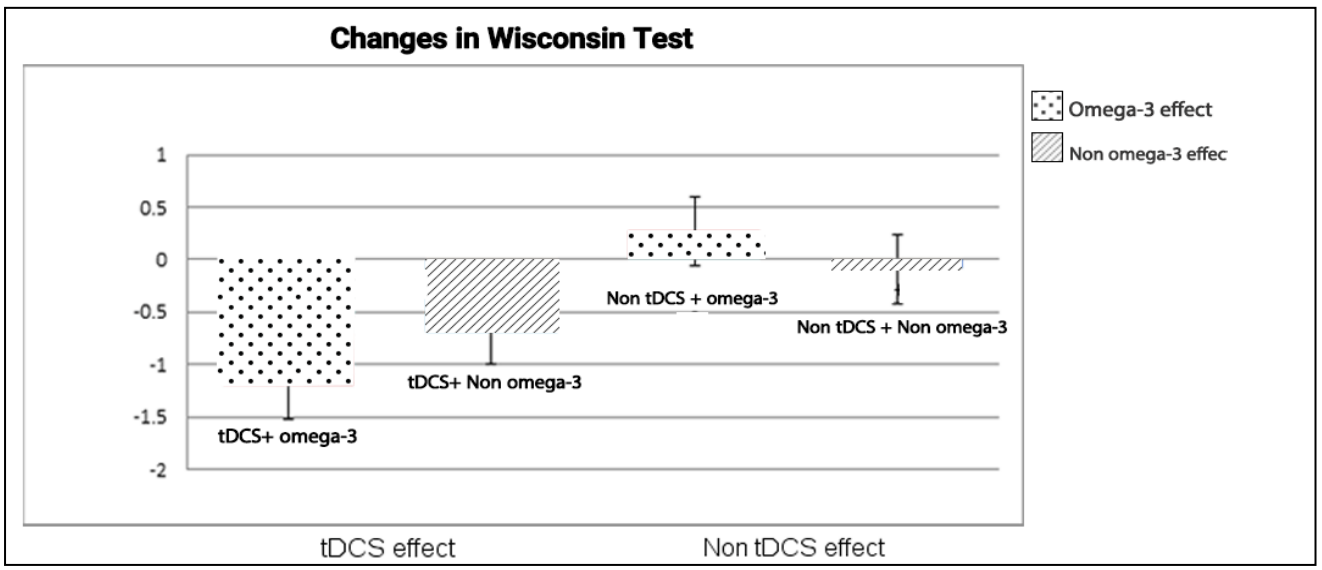

Figure 3. Interaction of Wisconsin Computer Test Changes (Improving Executive Function) in Stimulation and non-Stimulation of tDCS and Consumption and non-Consumption of Omega-3; Error Bars: 95% Confidence Intervals.

The results of the mean of the Wisconsin test scores on stimulation/non-stimulation of tDCS and consumption/non-consumption of omega-3 are presented in Figure 3. The outcomes indicate that clients exposed to the tDCS stimulation adjunct with the omega-3 intake had higher performance in all indices in comparison with the control group and each treatment alone. These findings were clinically important.

At the end of the research, according to the side effects reporting questionnaire completed by the participants, the side effects were as follows:

In the group receiving both tDCS and omega-3, four cases reported side effects including itching, headache, anxiety, stress, forgetting, and tingling. In the group receiving sham and placebo, seven cases reported side effects including itching, headache, anxiety, stress, lethargy, vertigo, discomfort, insomnia, and irritation. In the group receiving sham and omega-3, four cases reported side effects including itching, headache, anxiety, stress, tingling, insomnia, discomfort, and irritation. In the group receiving tDCS and placebo, six cases reported side effects including itching, headache,

anxiety, stress, tingling, discomfort, and insomnia. There were no any significant differences between the groups regarding the side effects using the Chi-square test (P = 1.4, df = 3).

Discussion

This study potentially represents the first to explore the influences of DLPFC-tDCS (anode-left/cathode-right) combined with omega-3 on food craving, executive functions, and weight in patients with depression and overweight. Our findings revealed a significant interaction between tDCS and omega-3 in reducing body weight ($P < 0.01$). While other variables, including depression, did not show significant changes, we noted clinically important improvements in appetite, food craving, and executive functions (assessed by the WCST) with the addition of omega-3 to tDCS. The study's novelty lies in its hypothesis that omega-3's effects on depression and obesity symptoms are mediated through its accumulation in the DLPFC, leading us to use omega-3 as a supplement to enhance brain stimulation effects. Our factorial design trial distinctively evaluated the separate and combined impacts of tDCS and omega-3. Additionally, our approach of administering four stimulations in one session marks an innovative aspect compared to previous studies.

Our finding is consistent with the study of Usaos *et al*. (51) who assessed changes in appetite, weight as well as food cravings following brain stimulation. In their study, they analyzed 38 women (BMI $\geq$ 25) during eight sessions of tDCS (n = 20 active/18 sham) for four weeks. They used a 2-mA montage (20 min duration) for this purpose to increase the excitability of the left DLPFC adjunct with a diet (20 kcal/kg per day calorie). They assessed the executive-cognitive mechanisms through food-modified computerized tasks. They reported that the participants receiving tDCS stimulation significantly experienced more reduction in body weight compared to sham. Similarly, they reported a slightly higher decrease in hunger and food craving and a parallel improvement in task performance (especially the working memory and inhibitory control) in the tDCS group.

In our study, the synergy of tDCS and omega-3 led to weight loss, possibly through reduced appetite, food craving, and improved executive function (as measured by the WCST). This clinical relevance could shed light on the possible pathways for decreasing body weight. Probably, these positive clinical observations on appetite, food craving, and improvement in executive functions have led to weight loss in female clients with depression and overweight. A difference between our study and most existing literature is a higher intensity ($\geq$ 2 mA) of stimulation in similar studies (14) and the fact that we performed four stimulations in one session. However, in compensating for this, the synergy with omega-3 caused to intensify the effectiveness of tDCS. In justifying this mechanism, the combination of omega-3 with tDCS intensified the effect of brain stimulation on improving cognitive functions and decreasing appetite, ultimately resulting in better weight loss. As we understand, high BMI and obesity are linked to neurocognitive deficits and decreased activity in the prefrontal cortex, which contributes to overeating and interferes with weight loss attempts; and the omega-3 and tDCS combination could target the DLPFC by increasing its activity and excitability, and through this mechanism, it may modify appetite (51). Actually, tDCS modifies cortical excitability by manipulating the resting potential on the neuronal membrane, resulting in neuronal signaling regulation (52). Recent studies have shown that tDCS could decrease appetite by increasing the excitability of the DLPFC and regulating the dopaminergic system (53). Furthermore, previous studies have indicated that omega-3 could modify the fluidity of the neuronal membrane, regulation of neurotransmission, and production of bioactive mediators. In this way, it could be concluded that the omega-3 could enhance the effectiveness of tDCS, and they together are able to increase the stimulation in the PFC, leading to decreasing food cravings, appetite, and ultimately weight loss. Therefore, omega-3 could increase the impact of brain stimulation and may enhance the effectiveness of tDCS in clients with obesity.

Furthermore, there is a connection between obesity and inflammation. Adipose tissue is known as the chief source of inflammatory cytokines in the body. On the other hand, the literature indicates that omega-3 could decrease various proinflammatory cytokines (54). Docosahexaenoic acid (DHA), one of the omega-3 components, is usually found in high concentrations in the neuronal membrane and play major roles in sustaining the normal brain structure and performance. Furthermore, DHA could play a key role in signal transduction and serve as a precursor for anti-inflammatory cytokines (52). Ozturk and colleagues examined the influence of omega-3 and tDCS, on the plasma inflammatory cytokines in clients with migraine. They assessed the cytokines which are involved in increasing or decreasing brain inflammation including tumor necrosis factor-alpha (TNF-α), vascular endothelial growth factor (VEGF), brain-derived neurotrophic factor (BDNF), and interleukin-6 (IL-6) (55). They assumed that omega-3 and tDCS may balance the pro- and anti-inflammatory cytokines connected to brain inflammations in patients with migraine. Overall, in this study, only TNF-α had a significant change in response to omega-3 alone and omega-3 and tDCS combination ($P < 0.019$) groups (52). According to these findings, we can take a similar look at the anti-inflammatory influences of omega-3 and tDCS in the brain and their role in reducing adipose tissue-induced inflammation in obese subjects. In this way, omega-3 and brain stimulation each may have anti-inflammatory

influences on the brain, and their combination could intensify these effects. This is a hypothesis and requires more careful research, especially in the field of obesity.

The reports of omega-3 effects on depression are controversial and uncertain in the existing literature. There is a belief in the general population that omega-3 intake could protect against depression. Keshavarz *et al.* wanted to assess the influences of daily six capsules of omega-3 (every capsule contains 180 mg EPA, and 120 mg DHA) for 12 weeks on body weight and depressive signs in women with obesity and depression compared to the placebo. They reported a reduction in depression symptoms and body weight compared with the placebo (41). Furthermore, other studies show that adding omega-3 to standard antidepressant medication (for 12 weeks) could significantly decrease the symptoms of depression. While previous trials reported a possible effect of omega-3, some trials reported no effect of omega-3 fatty acids on depression. For example, a recent meta-analysis demonstrated that omega-3 supplements have no benefit for depression (56). In our trial, we found no significant influence of omega-3 alone on depression. Furthermore, Vesco *et al*. aimed to determine the effectiveness of omega-3 supplements and a psychotherapy method, each alone and in combination, on executive functions in youths with mood disorders. They examined 95 adolescents in 12 weeks with two omega-3/placebo capsules per day (1.87 g, mostly EPA) and their families participated in the psychotherapy classes twice a week and the results showed that omega-3 consumption groups (alone and combined) reported a significant improvement in executive functions (57). These results were inconsistent with our results probably because of the shorter duration of our trial. On the other hand, Rangel-Huerta and colleagues evaluated the pooled estimate of the effect sizes of the omega-3 intake on cognition in a meta-analysis of RCTs and concluded that it is unclear whether omega-3 could decrease cognitive decline, which was consistent with our results (58). Variety in response to omega-3 could be possibly due to many factors including biological and genetic differences among patients as well as study duration, dosage of omega-3, the severity of disease, and different assessment tools.

Similarly, we faced this challenge regarding the effectiveness of tDCS on outcome variables. In the study of McClintock *et al.* (59) 130 participants with depressive disorders were randomly allocated to high intensity (2.5 mA for 30min) or low intensity (0.034mA, for 30min) tDCS for 20 sessions over four weeks. Anode electrode was positioned over the left DLPFC at F3 and the cathode over F8. They assessed neurocognitive and clinical variables pre- and post-tDCS. Participants in both groups improved in executive functions. They concluded that tDCS could be effective in neurocognition among patients with depressive disorders.

Rezaei *et al.* included patients with major depressive disorder in two different tDCS protocols. In this study, 84 participants underwent 10 sessions of 2-mA daily tDCS (lasted for 20 min) and 32 patients received 10 sessions of 2 mA tDCS twice daily (lasted for 20 min). The anodal electrode was positioned over the left DLPFC, and the cathode was located over the right supraorbital area. They assessed the symptoms of depression by the BDI-II before and after the tDCS intervention. In this study, 47.4% of participants improved in symptoms of depression which were moderated by cognitive functions (60). However, in our research, we did not find statistically significant influences of tDCS on depression and executive functions. The severity of depression could be a reason for different observations between our study and others. Furthermore, previous studies revealed that inter-individual variances in COMT and BDNF polymorphisms may affect neurocognitive outcomes following the tDCS stimulation (59). Similar to our findings, Stevens *et al*. concluded that tDCS stimulation on the DLPFC (20-min 2 mA) on 28 subjects with overweight and obesity could not significantly decrease food craving (61). Furthermore, in a similar study on the effect of DLPFC stimulation on 28 overweight clients, participants received 20 sessions of tDCS for four weeks along with a low-calorie diet and reported that although the weight loss in clients who received tDCS was larger than the control group, the difference between groups was not statistically significant (62).

Generally, in comparison with similar studies, the reason for the lack of significant change in some variables of our study could be attributed to the differences in the study methods, tDCS protocol, omega-3 dose, or the subjects' severity of disease and different polymorphisms. The other reason for the inconsistency could be found in the research limitations (lack of statistical population). The other difference between the present study and others is in the number of stimulation per session (four sessions per day). We chose this protocol to increase the feasibility of the study. This protocol could be welcomed by practitioners due to the convenience of the patients compared to other protocols. Also, the intensity of the stimulation current in this study was decreased to 1.5 mA, which in other studies was 2 to 2.5 mA, so it is possible that the effect of transcranial stimulation has been compromised.

Limitation

From January 2020 to June 2020, due to the outbreak of the corona virus disease and frequent closures, the process of sampling stopped completely. As a result, patients were referred to the study site with a lot of stress and fear of the corona disease and some of them stopped the treatment during the study with the appearance of corona symptoms. The small sample size, lack of generalizability to the male community, and lack of

access to patients with major depression were some limitations of the current research.

Conclusion

In summary, the results of this RCT confirmed a significant interaction effect of tDCS and omega-3 in reducing the weight of women with depression and overweight. Furthermore, we observed a greater clinical improvement in the combined group regarding executive functions and appetite compared with the control group. However, the changes were not statistically significant in tDCS or omega-3 alone regarding food craving, depression symptoms, and executive functions. tDCS could strengthen the omega-3 mechanisms of effect through stimulating its accumulation site in the brain (i.e., DLPFC) and synergistic effects of these two treatments result in weight control as well as an improvement trend in the executive functions and food craving in women. Future studies with larger sample sizes and more diverse populations should be conducted to validate the findings of this study.

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Conflict of Interest

None.

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