

## The Effectiveness of Transcranial Direct Current Stimulation (TDCS) on Anxiety, Depression, and Physical Symptoms of People with Chronic Pain

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### Abstract

**Introduction:** Chronic pain and the experience of living with it are unique. Individual's perception of pain is affected by physical, psychological, and social variables. This study aimed to determine the effectiveness of transcranial direct current stimulation (tDCS) on anxiety and depression and physical symptoms of patients with chronic pain.

**Method:** This study was a semi-experimental study with pre-test, post-test, control group and follow-up phase. The statistical population of the study included all men and women referred to outpatient medical centers in Tehran in 2019. Among them, 30 subjects were selected by convenient sampling method and randomly assigned to experimental and control groups. Data were obtained using the Beck depression questionnaire and the Beck anxiety questionnaire. Repeated variance analysis was used to analyze the data. The above analysis was carried out using SPSS.22 software.

**Result:** The results showed that the transcranial direct current stimulation (tDCS) was effective in decreasing anxiety ( $F=8.97$ ,  $P<0.01$ ), depression ( $F=5.27$ ,  $P=0.03$ ) and physical symptoms ( $F=4.20$ ,  $P=0.04$ ) of people with chronic pain.

**Conclusion:** It can be concluded that stimulation of the posterior-lateral region of the left prefrontal cortex and posterior-lateral region of the right prefrontal cortex can normalize anxiety and depression states.

**Declaration of Interest:** None

**Keywords:** Chronic pain, Physical symptoms, Depression, Anxiety, Transcranial direct current stimulation.

## ***Introduction***

Chronic pain and the experience of living with it are unique. Individual's perception of pain is affected by physical, psychological, and social variables (1). The International Association for the Study of Pain (IASP) defined chronic pain as an unpleasant sensory and emotional experience associated with real or potential tissue damage (2). Pain is essentially divided into two acute and chronic types in terms of duration. Acute pain is described as pain with rapid and short-term onset. This pain plays a protective role that informs the person about the injuries and causes the movements to move away from the unpleasant stimulus. Chronic pain is a common problem that causes huge challenges for therapists due to its complex nature, ambiguous etiology, and poor response to treatment (2). Physical symptoms of chronic pain include mild to severe pain that is not relieved as expected and pain can be instantaneous (such as gunshots), burning, normal pain, or such as electrocution, and contusion, heaviness, or cramping (3). Kuner & Flor (4), have suggested that chronic pain is one of the most common and debilitating chronic health issues. Chronic pain is a major health-related problem in the world and seriously affects the quality of the social and occupational life of patients. The results of studies in Iran also indicate that this problem has a high prevalence and leads to psychological distress (5).

One of the reasons that chronic pain is one of the most problematic diseases of the present era is its comorbidity with physical diseases and mental disorders (6). There are countless epidemiological studies that supports the high prevalence of major psychiatric disorders among patients with chronic pain. The most

common psychiatric disorders are comorbidity with chronic pain, depression (10-100%), anxiety (with higher prevalence of depression), sleep disorders, drug addiction (with higher prevalence than the general population) (7). Anxiety entails an insecure concept or threat that one does not clearly understand the source of threats, and is perceived as a threatening situation influenced by increased stimulation, both internal and external, that one is incapable of controlling (8). The second most common psychiatric diagnosis in these patients is a depressive disorder. Most patients experience periods of denial and hopelessness followed by symptoms of depression and anxiety (9).

Medications for mild pain and occasional pain can be used such as acetaminophen, aspirin, or ibuprofen (10). Despite the moderate effectiveness of some pharmacological and psychological treatments for pain, chronic pain remains a stressful and debilitating disease for many, and there is no complete and successful treatment for it (11). In recent years, research on the effectiveness of noninvasive brain stimulation techniques has increased (12). The principles of this work are that two electrodes, one positive pole and the other negative pole, are placed on the head through a sponge pad soaked with the conductive solution. After passing through different areas (scalp, skull, etc.), the electrical charges by these electrodes reaches the surface of the cerebral cortex. The electrodes that has reached this region causes neurons to have an electrical charge and creates a positive and negative pole that leads to changes in the activity of the area (13). According to reviewing the available resources, it seems that no research has been conducted in the country comparing the effectiveness of acceptance and commitment therapy and drug

therapy and transcranial direct current stimulation on psychological distress (anxiety and depression) and physical symptoms of people with chronic pain. This study aimed to determine the effectiveness of transcranial direct current stimulation (tDCS) on anxiety and depression and physical symptoms of patients with chronic pain.

### **Methods**

This study was semi-experimental research with pre-test, post-test, and follow-up with the control group. The statistical population consisted of all men and women referred to outpatient medical centers in Tehran in 2020 who had received a definite diagnosis of chronic pain by neurologists and rheumatologists. Therefore, the study community selected all patients with chronic pain who were eligible based on inclusion and exclusion criteria. Considering the effect size of 0.40, confidence level of 0.95, test power of 0.80, and loss of 10% for each group, 30 people were calculated. Inclusion criteria included the definitive diagnosis of chronic pain based on medical records and by a specialist physician, age range of 30 and 60 years, not receiving pre-psychological treatments up to 6 months before the study, lack of personality disorders, and psychosis, and lack of substance abuse and dependence. Exclusion criteria were non-compliance with the group rules stated in the first session and absence in more than two sessions. The experimental group received admission and commitment therapy in eight sessions of 90 minutes and once a week for two months, but the control group did not receive any treatment. Both groups responded to the research questionnaires in three stages: pre-test, post-test, and follow-up (two months after the post-test).

The sampling method in this study had two stages: first, 97 people were selected from several people with a definite diagnosis of chronic pain through convenient sampling and then, based on inclusion criteria and conducting a pre-test session with a clinical interview conducted by the researcher under the supervision of a psychiatrist and based on DSM-5 diagnostic criteria, 60 (for each group of 30) of the women and men with the highest scores (as the highest scores) Baseline) after completing the questionnaires, they were selected by simple random sampling method and after random allocation was replaced in two groups of intervention (30 persons) and control (30 persons). The ethical considerations of the present study were as follows: 1- All participants received oral information about the research and if they wish to participate in the research. 2- Participants were assured that all information is confidential and will be used for research affairs. 3- To respect privacy, the participants' names and surnames were not registered. 4- To ensure the process, all questionnaires were conducted by the researcher himself. This article has the code of ethics committee number IR.HUMS.REC.1399.233 is from Hormozghan University of Medical Sciences.

### **Measurement**

**Beck Depression Inventory:** Beck Depression Inventory is the second edition developed to measure the severity of depression based on DSM-5 depression criteria. The questionnaire consisted of 21 questions, each of which consisted of four grading options between 3-2-1-0, with the total scores ranging from 0 to 63, with the high score being a sign of greater severity of depression. The cut-off point in the Beck depression questionnaire was 13. The test

reliability of one of its sevens was 0.93 and the internal consistency via Cronbach's alpha was 0.91 (14). Also, construct validity based on the convergent validity calculation method has been calculated the correlation coefficient of scores obtained from the second edition of Beck depression and depression scale of brief index questionnaire which showed a correlation of 0.87. In research conducted by Toosi et.al (15) the simultaneous validity of correlation coefficient between the mean of the first 20 questions and with question 21 was 0.83 and in the content validity of the validity coefficient of the total questions of the depression, the questionnaire was calculated 0.85. The validity and reliability of this questionnaire in the present research were 0.73 and 0.79, respectively.

**Beck Anxiety Questionnaire (BAI):** Beck et.al (16) introduced this questionnaire which specifically measures the severity of clinical anxiety symptoms in people. In each article, one of the four options that indicate the severity of anxiety is chosen. The four options for each question are scored in a four-part spectrum from 0 to 3. Each test material describes one of the most common symptoms of anxiety (mental, physical, and phobia symptoms). Therefore, the total score of this questionnaire ranges from 0 to 63. Its internal consistency coefficient (alpha coefficient) is 0.92, its validity varies from 0.30 to 0.76 by re-trial method with an interval of 0.75 weeks and the correlation of its materials varies from 0.30 to 0.76 (16). Kaviani and Mousavi (17) reported the validity coefficient of 0.72 and the validity coefficient of the test between 0.83 and 0.92 Cronbach alpha in the Iranian population. The validity and reliability of this questionnaire were 0.77 and 0.82, respectively.

**McGill Pain Questionnaire (MPQ):** In 1997, the McGill pain questionnaire was constructed by Melzack et al. (18) and has 20 items and aims to measure people's perception of pain from different dimensions of pain (sensory perception of pain, emotional perception, perception of pain assessment and various pains). McGill pain questionnaire is one of the most prominent pain measurement tools that has been used for the first time by Melzack and on 297 patients who have suffered from different types of pain. The McGill Pain Questionnaire consists of two independent factors, one entitled Sensory Pain that describes the experience of pain in person, and the other emotional pain that describes the emotional impact of experiencing pain. Obtaining higher scores in this questionnaire means more pain perception in the individual (18). In Mehdizadeh et.al (19) research, Cronbach's alpha coefficient for all components was between 0.83 and 0.87. The validity and reliability of this questionnaire in the current study were 0.75 and 0.79, respectively.

**Transcranial Direct Current Stimulation (TDCS)** TDCS is a painless and safe procedure performed by electrodes of one or two milliamperes in a limited time of twenty to thirty minutes by electrodes fixed on the skull. This current modulates the activation of a part of the cerebral cortex located below the electrode and affects the excitability, synaptic flexibility, or activation of a specific part of the brain.

Depolarization flow - The higher the electric charges, the greater the impact we expect to see. However, due to the safety of the subjects in this study, the current intensity is adjusted up to 2 mA.

Shape and size of electrodes - The density of current flowing through the skull is of particular importance. Density, or current density, represents the amount of current passing through each square centimeter of the electrode. In most studies, the current density is adjusted from 29% to 08% mA per square centimeter. Based on this, the shape and size of the electrodes will be affected. In this research, 25 cm electrodes are used and to establish a proper connection between the electrodes and the skull, wetting the pad on the electrode, which is made of fabric, with salt water is used.

Duration of the plan and the interval between stimulation sessions. In this study, the duration of stimulation is 20 minutes, and the number of stimulation sessions is repeated for 12 weeks in 6 weeks. The interval between them is set between 3 to 7 days.

Stimulation Protocol: In this protocol there are two active excitation circuits and the electrodes are placed in positions cz-f3-f4 according to standard 10-20. Position cz is considered as the reference (base), one of the

activation channels is activated between cz and f3. The sine waveform has a frequency of 10 Hz and a range of 1 mA with a negative cathode current of 1 mA. Another activation channel is activated between cz and f4. The sine waveform with a frequency of 10 Hz and a range of one milliamperere with a positive anode current is about one milliamperere.

Data were analyzed using mean and standard deviation and repeated measure ANOVA and SPSS.22 software.

### Results

The mean age of participants in the experimental group were 43.7 (8.9) and in the control group was 45.2 (9.2). In the experimental group, 16 (53.3%) were women and 14 (47.7%) were men, and in the control group, 14 (47.7%) were women and 16 (53.3%) were men. The results show that the two groups are almost homogeneous in age and gender variables. The results of the Chi-square test also show that the difference between the two groups in terms of age and gender was not significant.

Table 1- Mean (SD) variables of depression, anxiety, and Physical symptoms by measurement stage in groups

Variables	Group	Pretest		Post-test		Follow-up	
		M	SD	M	SD	M	SD
Depression	Intervention	34.80	5.70	27.33	3.83	26.80	4.71
	Control	33.73	5.01	33.33	7.39	35.07	7.52
Anxiety	Intervention	32.00	4.41	25.60	3.79	27.07	4.77
	Control	34.00	4.47	32.53	7.03	32.93	5.65
Physical symptoms	Intervention	40.13	3.07	35.47	3.96	35.07	2.69
	Control	40.40	3.14	38.13	4.98	39.73	5.55

To investigate the significance of the difference between the experimental avoidance score in the two emotion regulation groups and the control group, an analysis of variance with repeated measurements was used. Before repeated measurement analysis of variance test, the results of M box, Mauchly sphericity, and Leven's tests were evaluated. Since the M box test was not significant for any of the research variables, therefore, the homogeneity condition of the variance-covariance matrix was properly observed. Also, the lack of significance of any of the

variables in Leven's tests showed that the condition of equality of intergroup variances was observed and the variance of dependent variable error in all groups was equal and finally, the results of Mauchly sphericity showed that this test was also for the experimental avoidance variable. Therefore, the assumption of the equality of variances within-subjects (spherical assumption) was not observed (Mauchly's  $W=0.55$ ,  $P>0.05$ ). Therefore, the Greenhouse Geiser test is used to evaluate the results of the univariate test for between-subject effects and interactions.

Table 2- Repeated measure analysis of variance to investigate the effect of time and group on depression, anxiety, and physical symptoms

Variables	Effect source	SS	df	MS	F	P	Eta
<b>Depression</b>	Time	269.42	1.57	171.24	13.43	0.001	0.32
	Time*Group	355.47	1.57	225.93	17.72	0.001	0.39
	Group	435.60	1.00	435.60	5.27	0.03	0.16
<b>Anxiety</b>	Time	253.42	1.42	178.78	14.15	0.001	0.34
	Time*Group	101.07	1.42	71.30	5.64	0.01	0.17
	Group	547.60	1.00	547.60	8.97	0.01	0.24
<b>Physical symptoms</b>	Time	205.96	1.62	127.18	14.23	0.001	0.34
	Time*Group	72.80	1.62	44.96	5.03	0.02	0.15
	Group	144.40	1.00	144.40	4.20	0.04	0.13

The results of Table 2 showed that analysis of the variance of depression variable was significant for the effect of time ( $P<0.001$ ) and the effect of group ( $P<0.001$ ) and the effect size of a group intervention for this depression was 0.39. Analysis of variance of anxiety variable was significant for the effect of time ( $P<0.001$ ) and the effect of group ( $P<0.001$ ) and the effect size of a group intervention for anxiety was 0.36. Analysis of variance of physical symptoms variable was significant

for time effect ( $P<0.001$ ) and group effect ( $P<0.001$ ) and the effect size of a group intervention for physical symptoms was 0.24. This meant that both variables of depression, anxiety, and physical symptoms were significantly different between the two experimental and control groups during the research phases, indicating the effect of the intervention.

Table 3- The results of Bonferroni's follow-up test for paired comparison of the meantime of measuring the research variables

Variable	Steps		Mean difference	Standard error estimates	P-value
<b>Depression</b>	Pre-test	Post-test	-4.46	1.11	0.001
		Follow-up	-3.33	1.11	0.001
	Post-test	Follow-up	1.13	0.59	0.105
<b>Anxiety</b>	Pre-test	Post-test	-2.26	0.51	0.001
		Follow-up	-1.93	0.51	0.001
	Post-test	Follow-up	0.33	0.53	0.804
<b>Physical symptoms</b>	Pre-test	Post-test	-2.26	0.51	0.001
		Follow-up	-1.93	0.51	0.001
	Post-test	Follow-up	0.33	0.53	0.804

The results of Table 3 showed that the score of depression in the experimental group and the post-test stage were lower than the pre-test ( $p < 0.001$ ). The results showed that depression at the follow-up stage had a significant difference from the pre-test stage ( $p < 0.001$ ). The results also showed that the scores of anxiety variables in the experimental group and the post-test stage were lower than the pre-test ( $p < 0.001$ ). Anxiety in the follow-up stage had a significant difference from the pre-test stage ( $p < 0.001$ ). The results showed that the scores of physical symptoms variable in the experimental group and the post-test stage were lower than the pre-test ( $p < 0.001$ ). Physical symptoms in the follow-up stage had a significant difference from the pre-test stage ( $p < 0.001$ ), but there was no significant difference between the post-test and follow-up stages. The results indicated that the effectiveness of acceptance and commitment therapy in the follow-up stage was persistent for both variables of depression, anxiety, and physical symptoms.

### Discussion

The results showed that the transcranial direct current stimulation had an effect on reducing depression in people with chronic pain than in

the control group. In line with this finding, George (20) concluded in a study on direct transcranial electrical stimulation in the treatment of depression that this treatment treated depression and reduced its symptoms.

In explaining the effectiveness of tDCS on reducing anxiety and depression, it can be said that the right prefrontal cortex (especially the amygdala) is hyper stimulated in people with chronic pain, while the left prefrontal cortex is aroused. Therefore, right DLPFC cathodal stimulation (inhibition) leads to decreased processing of negative emotions and anodal stimulation (increased activity) of left DLPFC leads to increased processing of positive emotions. Because the right hemisphere is more responsible for negative emotional processing and the left hemisphere is more responsible for positive emotional processing. In addition, the effectiveness of tDCS on depression is associated with other mechanisms (21).

According to the results of this study and research background, it seems that depression is more associated with DLPFC function. DLPFC is one of the main areas of the central executive network. Two networks are involved in rumination: central executive

network (CEN) and default brain state network (DMN). In line, Kalu et al. (21) showed that high levels of DMN activity were associated with high levels of depressed intellectual thirst and low levels associated with adaptive thinking styles. Along with the increase in DMN activity associated with rumination activity, the CEN network is starting to increase its activity. For this reason, DLPFC can play a key role in the balance between these two networks and thus optimize thinking.

Sequential stimulation of DLPFC in both hemispheres has a significant effect on depression. DLPFC stimulation in the right hemisphere affects intellectual thirst through modulation of cognitive processing and negative emotional information and in the left hemisphere through increasing cognitive control. Therefore, tDCS has a contrasting effect on right and left DLPFC, tDCS on left DLPFC increases cognitive control over positive information relative to negative information. Left DLPFC stimulation, despite increasing cognitive control, affects positive emotional information on electrophysiological activities and increases the amplitude of N450. The ACC's main function is to monitor conflict situations and provide an appropriate response, stimulating the left DLPFC activates the ACC-DLPFC circuit and helps reduce rumination through cognitive control and conflict resolution (21).

The results of data analysis showed that the transcranial direct current stimulation had a greater effect on reducing depression in people with chronic pain than in the control group. In line with this finding, George (20) reported that transcranial direct electrical stimulation reduced anxiety. In a study, Kalu et al. (21) concluded that stimulation of the right or left

prefrontal cortex reduced anxiety. Stimulation of the posterior-lateral region of the left prefrontal cortex and posterior-lateral region of the right prefrontal cortex can normalize anxiety states. Consequently, based on the mechanisms explained, direct electrical stimulation from the skull is effective in reducing the symptoms of social anxiety in patients with chronic pain.

The results of data analysis showed that the transcranial direct current stimulation had a greater effect on reducing depression in people with chronic pain than in the control group. Previous researchers also believe that electrical stimulation of the prefrontal cortex activates the dopamine neurotransmitter and increases it in this region and is associated with cognitive flexibility and improves function in people with physical symptoms. On the other hand, it has been found that the ability of cognitive flexibility allows simultaneous consideration of contradictory representations of an object or event when confronting new stimuli and environmental requirements (22). Therefore, it seems that this can explain the deficiencies in the ability of these patients, which has been proposed in the theory of mind as one of the etiology hypotheses in cognitive distortions, which means that therapists can reduce cognitive distortions, increase positive mental states of patients and reduce behavioral symptoms and treat them.

Some brain imaging studies have shown that 4 sessions of electrical stimulation therapy improved working memory-based neural communication in adults and provides long-term benefits by modulating cognitive function (23). Other researchers have reported that lateral posterior prefrontal cortex antic stimulation can improve the accuracy of

performance in letter order tests in healthy subjects and numbers hyper nation test in patients with major depression after 5 sessions of stimulation (24). The difference in the findings of some studies can be due to differences in the number of treatment sessions, intensity, duration, and location of stimulation, which even affects the rate of quitting. Rahmanian (25) reported that the higher the current density, the lower the rate of side effects but the higher rate of research withdrawal by the subjects, so commenting on this issue requires further and careful investigation in future clinical research.

The first and one of the most important limitations of this study was the use of a voluntary non-contingent sampling method for selecting subjects. During the sessions, the type of cooperation and willingness of the participants of the groups in the field of treatment was not completely the same, which is one of the limitations of the study. In this study, only a questionnaire was used to collect data and due to executive constraints, interviews were not used to collect the research data. Considering the first limitation, it is suggested that fewer error sampling methods such as random methods be used in future studies. For this purpose, questionnaires can be administered to a large group of people with chronic pain and several people who scored higher in depression and anxiety can be selected randomly. Another limitation was the use of self-report tools for data collection, so it is recommended that researchers use interviews in future studies to collect more accurate and valid data along with questionnaires or instead of questionnaires. It is suggested that researchers conduct this study on patients with other chronic diseases and compare the results with the results of this

study to discuss the generalization and effectiveness of the results more accurately and reliably.

Considering the effectiveness of treatment methods based on acceptance, commitment, and transcranial direct current stimulation on reducing depression, anxiety, and physical symptoms in patients with chronic pain, it is suggested that clinical psychologists and therapists use treatment methods based on acceptance, commitment, and transcranial direct current stimulation in their interventions, especially in the field of these variables. Considering the efficiency and applicability of treatment methods based on acceptance, commitment, and transcranial direct current stimulation and no significant difference between them in physical symptoms, it is suggested that managers and officials of health centers and psychological service centers, and clinics provide the necessary platforms for the use of treatments based on acceptance, commitment, and transcranial direct current stimulation. It is recommended that health authorities and planners in the province or country hold workshops based on acceptance and commitment for patients with chronic pain to reduce anxiety and increase positive psychological characteristics. The latest proposal is based on the effectiveness of both treatment methods on reducing depression so that managers and managers of psychological services centers and clinics require their counselors and therapists to pass treatment courses based on acceptance, commitment, and transcranial direct current stimulation so that they can use these methods in their interventions.

In conclusion, it can be said that research evidence suggests that transcranial direct

current stimulation can cause cortical changes in the brain even after the end of stimulation, appropriate and low-cost intervention to improve executive functions and with lower relapse rate to reduce physical symptoms, so it is necessary to use this type of intervention as a safe method in addition to using it for cognitive rehabilitation and prevention of disorders in psychiatric centers and counseling. Attention should be paid to psychotherapy for patients even for healthy people.

### Conflict of interest

The authors did not declare any conflict of interest.

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