Razavi Int J Med. 2024 August 12(3): e1327 doi: 10.30483/rijm.2024.254527.1327

Published online 2024 August **Original Article**

Comparing the Effect of Kootker's Cognitive Behavioral Therapy Combined with Transcranial Direct Current Stimulation or Pharmacotherapy with Citalopram on the Improvement of Depressive Symptoms and Working Memory in Stroke Patients: A Randomized Clinical Trial with a Three-month Follow-up

Elahe Moshtaghi[1], Mohammad Hossein Bayazi[1,*], Behzad Rigi Koote[2]

[1] Department of Psychology, Torbat-e Jam branch, Islamic Azad University, Torbat-e Jam, Iran
[2] Department of Clinical Psychology (Child and Adolescent Health Research Center), Zahedan University of Medical Sciences, Zahedan, Iran

*** *Corresponding author:*** Mohammad Hossein Bayazi, Department of Psychology, Torbat-e Jam Branch, Islamic Azad University, Torbat-e Jam, Iran. Tel: 09151679599; Email: brkpsycho1988@gmail.com

Received 2024 April 21**; Accepted** 2024 June 27.

Abstract

Background: Stroke is the leading cause of severe physical and cognitive disability across the globe.
Objectives: The present study sought to compare the effect of Kootker's cognitive behavioral therapy (CBT) combined with transcranial direct current stimulation **(**tDCS) or pharmacotherapy with citalopram on the improvement of depression symptoms and working memory of stroke patients.
Methods: In this study, we adopted a quasi-experimental pretest-posttest control group design. The population of this study included all stroke sufferers who were referred to a neurology clinic in Zahedan in 2022. Among this population, 45 cases were selected via the available sampling method and randomly assigned to three groups (n=15). To assess depression, Beck's Depression Inventory and N-back tests were employed at pre-test, post-test, and 3-month follow-up. The first experimental group underwent CBT and 20 sessions of anodal stimulation of the dorsolateral prefrontal cortex, while the second experimental group underwent CBT and 10 mg citalopram daily. The control group did not receive any intervention.
Results: The results of mixed analysis of variance highlighted the short-term and long-term effectiveness of both interventions in the improvement of depression symptoms of stroke patients (P<0.05), and no difference was observed between the efficacy of the two combined interventions. Furthermore, the combined intervention of CBT and tDCS had a short-term effect on the improvement of working memory.
Conclusion: As evidenced by the obtained results, it can be concluded that both combined interventions can be of great help in improving depression symptoms among stroke sufferers.

Keywords: Citalopram, Cognitive behavioral therapy, Pharmacotherapy, Stroke, Symptoms of depression, Working memory

1. Background

A stroke, also known as a cerebrovascular accident, occurs when the blood supply to parts of the brain is interrupted or reduced, preventing brain tissue from receiving essential oxygen and nutrients. This interruption can be caused by a blockage (ischemic stroke) or the bursting of a blood vessel (hemorrhagic stroke). As a result, brain cells begin to die within minutes, leading to potential long-term disability or death if not promptly treated (1). Stroke is responsible for 5.2% of all deaths worldwide and results in severe disabilities in survivors; therefore, it is considered the most important cause of disability (2).

Depression and neuropsychological disorders are prevalent after strokes. Neuropsychological disorders are recognized as the primary cause of death and severe complications after stroke. Approximately 30% of stroke survivors develop depression, and approximately 70% of these individuals suffer from neuropsychological disorders, which impose a heavy burden on medical care systems and patients. The occurrence of depression in these people is associated with higher mortality, poorer recovery from stroke, more obvious cognitive deficits, and lower quality of life compared to stroke without depression (3, 4). Post-stroke depression is often described as a depressive syndrome that usually appears a relatively short time after the stroke; nonetheless, it may have a late onset, beginning at least six months after the stroke. Update post-stroke depression is deemed a type of vascular depression since stroke may bring about the same pathophysiological changes as depression (5).

Despite numerous similarities between post-stroke depression and major depression, there are significant differences between the two disorders. The first difference is that the pathophysiology of depression after stroke is closely linked to the vascular damage caused by ischemic stroke. Second, more severe depressive symptoms are more likely to occur in post-stroke depression than in major depression. Third, the prevalence of specific symptoms of depression in these two disorders is somewhat different. For instance, post-stroke depression presents with more significant cognitive impairment, less anhedonia, and fewer disturbances in sleep cycle functioning than major depression. Fourth, people with post-stroke depression have a

disproportionately high prevalence of physical disability, such as aphasia, movement/gait impairment, and loss of sensory functions (3).

Recent studies demonstrated that depression occurs more frequently in stroke patients than in the general population. The mechanism of post-stroke depression is multifactorial and better explained by a combination of psychological, social, and biological factors (6). The location of the stroke in the brain has a significant relationship with the prevalence of post-stroke depression and cognitive dysfunction. In addition, emotional disorders, such as depression, are associated with cognitive impairment in stroke patients (7). Other studies pointed out that the pathophysiology of post-stroke depression is multifactorial and includes a combination of various neurobiological disorders caused by ischemia (8). The set of these relationships indicates that the occurrence of depression after a stroke is not the mere result of a psychological shock; instead, some physiological changes in the brain are also at play. Moreover, the latest studies indicated that the pathophysiology of post-stroke depression includes a decrease in the level of monoamines, an abnormal neurotrophic response, an increase in inflammation with a disturbance in the regulation of the hypothalamic-pituitary-adrenal axis, and a defect in the excitatory function of the brain mediated by glutamate, which are due to strokes occurring in the brain (3).

As mentioned before, in addition to depression, disorders in neuropsychological functions are also prevalent in people with stroke. Following the breaking of the blood-brain barrier that occurs in a stroke, cerebral capillaries undergo changes, which, along with nerve atrophy, are the most critical factors contributing to the neuropathology of neuropsychological disorders (9). Neuropsychological characteristics are usually identified by specific defects in memory and learning, working memory, executive actions, attention, and processing speed, which are evident in the background of a generalized cognitive defect (10). The current study investigated working memory, which is considered an essential executive function.

Based on the cognitive approach, working memory is the most critical cognitive function involved in the information-processing process, providing the basis for efficient psychological processing. Weakness or strength of working memory can set the stage for the occurrence or improvement of mental disorders. Studies have illustrated that improving working memory boosts mood and behavioral efficiency (11). In working memory, current experiences are associated with previously stored schemas. This system also temporarily stores information, stores the input data of the cognitive system in a standby form, and consists of two parts: the central executive part and sub-parts for temporary storage and processing of various types of content, including non-verbal and verbal content (12). In some cases, these disorders are progressive, and therefore, it is of great importance to deal with them (9).

Therefore, considering the multifaceted nature of post-stroke depression and the presence of physiological factors in the brain, in order to improve post-stroke depression, it is necessary to use combined approaches that include psychological and effective interventions for the physiological mechanisms of the brain**.** Current treatment strategies for patients with post-stroke depression include pharmacological, psychosocial, and neurological interventions. There is consensus that antidepressants significantly increase the response and speed of recovery in post-stroke depression compared to placebo. In addition, several studies have pinpointed the practical effects of psychotherapy. Neuromodulation using repetitive transcranial magnetic stimulation, direct current transcranial electrical stimulation, and novel psychosocial interventions are potentially helpful treatments that require further research (13); nonetheless, little research has been conducted on combination therapies.

Recent studies suggested that the most effective combined treatments to improve post-stroke depression can include a combination of pharmaceutical, psychological, and social interventions, as well as interventions focused on rehabilitation. Early diagnosis and appropriate management are critical to achieving better outcomes in people with post-stroke depression (3). The following section will briefly review cognitive behavioral therapy, drug therapy, and intervention with direct current transcranial electrical stimulation. Cognitive behavioral psychotherapy helps patients with post-stroke depression to regulate their emotions and achieve optimal levels of activity and performance. This intervention also helps sufferers maintain realistic and optimistic thinking. Compared to drug therapy, cognitive behavioral psychotherapy has a lower relapse rate and lacks any side effects (14).

In a study that examined the treatment of depression after stroke, Withers et al. (15) introduced cognitive behavioral psychotherapy as the primary method and antidepressants as routine care. Through a review of research, they demonstrated that cognitive-behavioral psychotherapy alone is effective in the treatment of post-stroke depression, and combining this method with antidepressants is more effective than taking antidepressants alone. Few studies have evaluated cognitive behavioral psychotherapy as ineffective for the treatment of post-stroke depression. Studies have revealed that if the onset of depression is nine months after the

stroke, cognitive behavioral psychotherapy is more effective than antidepressants, and if the onset of depression is six months after the stroke, antidepressants are more effective.

Results were inconclusive for the occurrence of depression less than six months after stroke. The findings of this review demonstrate that it is not possible to definitively conclude whether cognitive behavioral psychotherapy is more or less effective than antidepressants and whether a combination of both would be more effective (15). Regarding the use of medications in the treatment of depression after stroke, Zhang et al. (16) stated that despite the widespread use of selective serotonin reuptake inhibitors, norepinephrine serotonin reuptake inhibitors, and tricyclic antidepressants as the first line of medication, there is no specific drug with conclusive evidence for recovery from post-stroke depression. In addition, pharmacological therapy can increase the risk of blurred vision, sexual dysfunction, urinary retention, tremors, severe insomnia, hypotension, and cerebral hemorrhage.

In general, drug treatments, such as the use of citalopram and paroxetine, and the use of psychotherapy methods, especially CBT, should be considered first-line treatments, and brain stimulation techniques, despite the observed effects, need further research (13). Nonetheless, in recent decades, newer methods have been employed to manage a range of psychological and neurological disorders**.** Noninvasive brain stimulation techniques as tools that lead to the improvement of plasticity in the brain are considered valid options for improving depression after stroke (17). Studies have suggested that anodal tDCS over the left dorsolateral prefrontal cortex (DLPFC), in addition to significantly improving the patient's mood, completely alleviates central pains after stroke (18).

Studies have pointed out that the use of transcranial electrical stimulation, while side effects are rarely reported for them, can exert beneficial effects on the neural circuits of the brain (19). As suggested by related studies, electrical stimulation leads to the improvement of disorders through neurophysiological mechanisms, such as marked effects on the secretion of neurotransmitters in the brain. The results of studies indicated that the increase of excitatory synaptic transmissions through electrical stimulation of anodes with direct current probably facilitates the transmission of glutamate and modulates the transmission of gamma-aminobutyric acid in the cerebral cortex. On the other hand, it positively or negatively modulates the transmission activities of dopamine, serotonin, and acetylcholine in the central nervous system. These neural events induced by tDCS may alter the balance between excitatory and inhibitory inputs. In particular, transcranial electrical stimulation with multiple sessions of direct current is thought to promote/regulate the efficiency of information processing in cortical circuitry, inducing long-term potentiation by the pharmaceutical interventions synthesis of various proteins (20).

In fact, the main advantage of tDCS compared to neuropsychiatric medications is the absence of severe side effects. Transcranial electrical stimulation is considered a low-risk method capable of inducing therapeutic results within a few days, while neuropsychiatric medications require more time to exert their full effectiveness. Since tDCS devices are portable and relatively cost-effective, even self-treatment at home seems possible in the future (21, 22). This method promotes patient independence and reduces the need for long-term professional assistance, thereby reducing care costs (21).

Another advantage of tDCS is the durability of the effect due to the creation of neuroplasticity in the brain and the marked increase in the effectiveness of other accompanying interventions due to the increase in brain excitability at the cellular level. It seems that the reduction of neuroplasticity, the occurrence of neuroinflammation, and the reduction of neurogenesis play a critical role in the occurrence of depression after stroke (13). One of the desirable effects of transcranial direct current stimulation is increasing plasticity in the brain. Moreover, the results of systematic review studies and meta-analyses indicated that anodal tDCS leads to the creation of long-term potentials (23) and increasing excitability (24) in the brain.

The potential of using tDCS in creating changes in the brain has caused its effectiveness to be investigated in some studies on treatment-resistant interventions.

2. Objectives

In their study, Martin et al. (25) illustrated that transcranial direct current stimulation, along with emotional regulation training, can be used as a new method for people with drug-resistant depression. It is worth noting that the stated study was conducted on 17 people with depression whose disorder was resistant to antidepressants. The participants were trained in emotional regulation and direct current transcranial electrical stimulation for 18 sessions during six weeks. According to the aforementioned issues, the fundamental question of this research is whether there is a difference between the effectiveness of CBT with tDCS and CBT with drug therapy in improving depression symptoms and working memory in stroke patients.

3. Methods

Study Design

In this study, we adopted a quasi-experimental pretest-posttest control group design. The first group received CBT plus tDCS, while the second group received CBT along with citalopram. Nonetheless, the third group did not receive any intervention. Beck's depression inventory, as well as Stroop and go-no-go computer tests, were employed at pre-test, post-test, and three-month follow-up.

Participants

The statistical population of the current study included all stroke sufferers who were referred to Dr. Hashem Zahi Neurology Clinic in Zahedan in 2022. The sample size included 45 of these people who were selected via the available sampling method and were randomly assigned to three groups (n=15). The inclusion criteria entailed normal vision and hearing, a time elapse of less than a year since stroke, scoring above 14 in the Beck depression questionnaire, the age range of 20-50 years, and non-use of antidepressants while participating in the research. Moreover, in order to use tDCS, we considered other criteria, including absence of pregnancy, intracranial electrodes, cardiac pacemakers, epilepsy, and convulsions (26), as well as the non-use of carbamazepine and flunarizine due to the disruption of transcranial tDCS (27). On the other hand, the exclusion criteria were as follows: non-participation in two intervention sessions or starting to take medication during the study.

After sampling, the randomly selected subjects were placed in three experimental groups. The participants in all three groups completed three computer tests, and according to the program of the first and second groups, they were subjected to relevant interventions, while the third group did not receive any intervention. At the end of the interventions and after three months, two computer tests and the Beck depression questionnaire were administered again to all subjects in three groups. At first, 138 cases were initially evaluated to enter the study, and after checking the inclusion criteria, 57 subjects entered the study stages, and finally, the data of 45 cases were analyzed. A summary of the executed method is provided in Consort's flowchart (Figure 1)(28).

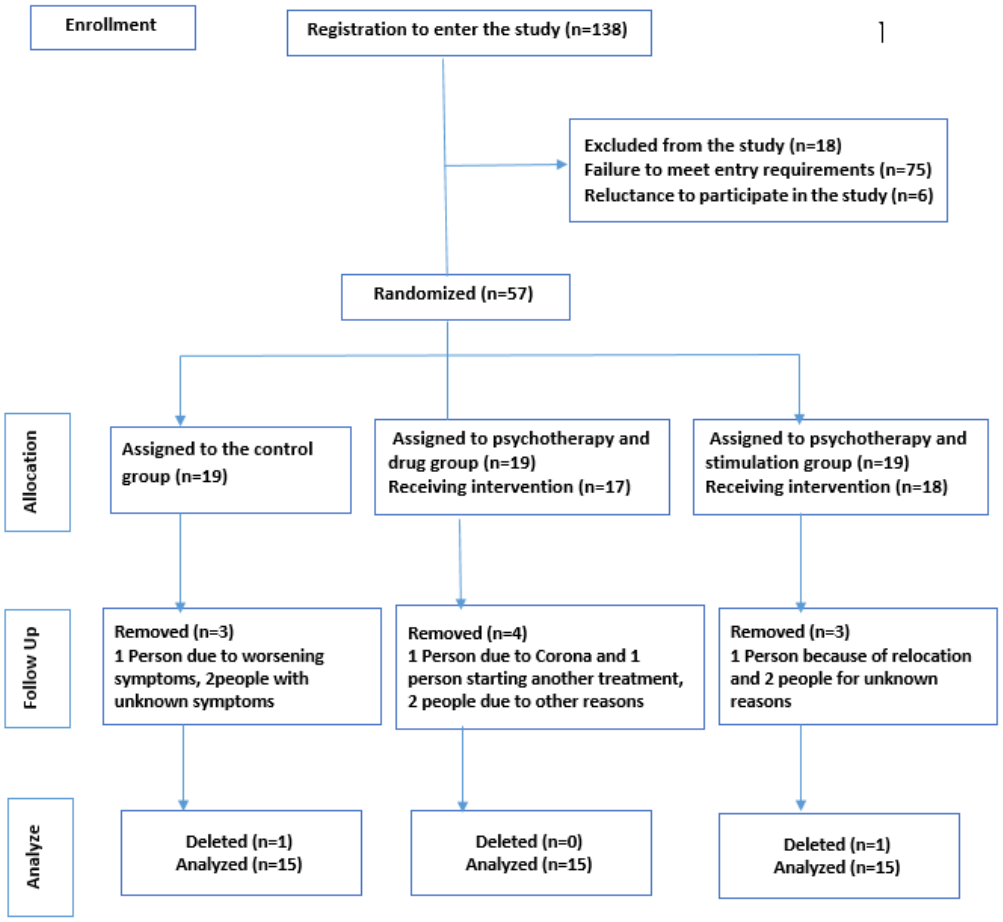

Figure 1: Consort flow diagram

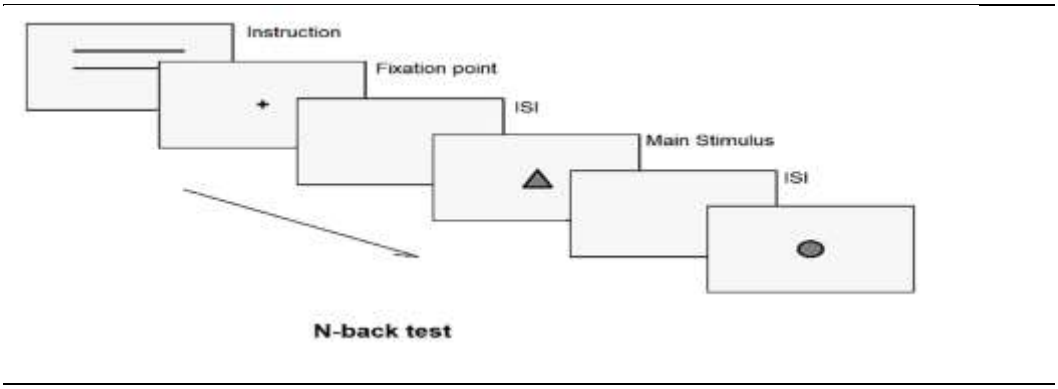

Figure 2. Steps of N-back test

Instruments

Beck Depression Inventory (BDI): This 21-item scale has a high ability to distinguish normal people from depressed ones and determine the severity of depression symptoms. The studies that were conducted reported the reliability coefficient of this questionnaire to be 0.73 (29). The items in this questionnaire are rated based on a four-point scale, ranging from 0-3. The final score varies between 0 and 63, with scores less than 13 indicating the absence of depression and the person's normality. Moreover, scores of 14-19, 20-28, and above 29 are suggestive of mild, moderate, and severe depression, respectively (30). In Iran, the validity of this questionnaire was investigated using the test-retest method, and it was reported as 0.78 (31).

N-back computer test: This test is used to measure working memory performance. In this test, a sequence of visual stimuli is presented to the subject step by step (Figure 2), and the subject must answer the question for each presented stimulus, whether this stimulus is the same as the stimulus one or more steps before or not. Answering this question requires keeping the latest stimuli presented and updating these stimuli; therefore, working memory will play an essential role in responding. Finally, the number of right and wrong answers shows the efficiency of a person's working memory. The components of this test are as follows: first, a "+" sign is displayed in the middle of the page for 500 milliseconds to draw the subject's attention to the middle of the page. After the display period of this stimulus, a white screen is displayed, and the main stimulus appears on the screen. During the presentation of the main stimulus, the subject must press the appropriate button in the shortest possible time if the stimulus matches one or more previous stimuli (according to the test phase) (28).

tDCS device: a two-channel stimulation device and silicon carbon pads with 5x7 cm dimensions placed in a spongy fabric cover were used. The direct current electric stimulation device has two electrodes, one of which is the anode with stimulation capability, and the other is the cathode electrode.

Interventions

Transcranial direct current stimulation device (tDCS): a two-channel stimulation device and silicon carbon pads with 5x7 cm dimensions placed in a spongy fabric cover were used. The tDCS device has two electrodes, one of which is the anode with stimulation capability, and the other is the cathode electrode. In the current study, the tDCS based on Li et al.'s protocol (32) for post-stroke depression was employed. The assembly used in this protocol was F3-F4 (according to the 10-20 system). The anode electrode was placed on the dorsolateral part of the prefrontal cortex, and the cathode electrode was positioned on the corresponding side. The intensity of current will be 2 mA, and the duration of stimulation will be 20 minutes for each session. The number of sessions was five sessions per week, and the intervention lasted for four weeks (20 sessions in total). In each session, the subject sat on a chair in a quiet place with a suitable temperature and refrained from sleeping or closing his eyes during the stimulation period. It is noteworthy that the beginning of therapeutic interventions was simultaneous. This means that tDCS, cognitive behavioral psychotherapy, and drug therapy started simultaneously in one week.

Kootker's Cognitive Behavioral Psychotherapy for stroke: This treatment protocol (Table 1) was designed for patients with chronic mood complaints after stroke. The treatment protocol of this intervention consists of 12 individual treatment sessions that include five consecutive stages (33).

Pharmacotherapy: pharmacotherapy was performed using Escitalopram, which was prescribed by a psychiatrist. Previous antidepressants (if any) were washed out. Citalopram 10 mg was prescribed for three weeks and consumed by the subjects in the respective groups. In addition, the use of benzodiazepines up to 20 mg of diazepam and its equivalent tablets was not prohibited (34).

Table 1. Kootker's Cognitive Behavioral Psychotherapy for Stroke

Stage	Subject	Session	Treatment method	Therapeutic technique
First: Assisting the client in recognizing the problem and acquiring information about post-stroke depression.	Familiarization and psychoeducation	1	Establishing rapport	Introduction, familiarization with the patient, and creating a safe space for disclosing problems
		2	Assessment and understanding of grief and loss	Discussion of grief, review of adherence to homework
		3	Psychological education	Motivational interviewing techniques to help patients discover what they want to achieve
Second: Goal setting	Goal setting	4	Goal setting considering ACS	Interviewing and using photos to discuss "past, present, and future
		5	Goal selection: Joint session between the psychologist and movement therapists	"Moving towards three achievable goals considering individual physical and cognitive capacities
Third: Examination of irrational cognitions and false beliefs	Cognitive therapy	6	Cognitive behavioral therapy introduction, diagnosis of hidden cognitions	Examine whether patients understand the three-step sequence. Filling out one or two examples with a patient to bring home.
		7	Reflection on hidden cognitions and their rational or irrational nature	We need to discuss the three-step sequence of homework tasks and introduce hidden cognitions or beliefs.
Fourth: challenging and correcting irrational cognitions and false beliefs challenging	negative cognitions	8	Challenging irrational beliefs	Motivational interviewing is used to support patients in coping with negative thoughts.
		9	Correcting cognitions	Supporting patients in replacing negative thoughts
		10	Correcting fixed beliefs	Therapists either help challenge thoughts or use the session for evaluation.
Fifth: Relapse Prevention	Preventing Relapse	11	reviewing signs of relapse and future strategies	Allowing patients to evaluate their acquired skills and goals. Supporting patients in areas they wish to improve.
		12	Summary and evaluation	Preparing patients for future situations. Creating a homecoming plan. Developing a four-stage follow-up for anticipated future situations.

The table presents the Kootker's Cognitive Behavioral Psychotherapy Protocol for stroke patients. It outlines five stages of the therapy, detailing the subject of each session, treatment methods, and therapeutic techniques. The stages include familiarization with the problem, goal setting, examining and correcting irrational thoughts and false beliefs, challenging negative cognitions, and relapse prevention. Each stage provides specific therapeutic techniques aimed at helping patients address post-stroke depression and cognitive difficulties.

Ethical Considerations

The current research was approved by the Ethics Committee of Islamic Azad University, Torbat Jam Branch (Code: IR.IAU.TJ.REC.1402.003) and the Clinical Trial Registration Center of Iran (Code: IRCT20230618058511N1).

4. Results

In the current research, the data of 45 subjects who were assigned to three groups (n=15) (two experimental groups and one control group) and measured three times (pre-test, post-test, and follow-up) were analyzed in SPSS software (version 29) using mixed variance analysis method.

Descriptive indicators, including age, gender, and marital status, are reported in Table 2.

The assumptions of using analysis of variance were investigated. In all variables of the research, the assumptions of normal distribution of subjects' scores, homogeneity of regression slope, equality of covariance matrix, and homogeneity of variances, which were examined by the Box's M test, were maintained ($P<0.05$). Therefore, there was no prohibition to use multivariate analysis of covariance and analysis of variance with repeated measurements.

The results of the mixed variance (Table 3) analysis indicate that time and group had a significant effect on depression symptoms, while the interaction of time and group did not have a significant impact on this variable. This signifies that depression scores are different, at least in the two groups. The results of the follow-up test illustrated that both the first and second test groups were significantly different from the control group, and there was no significant difference between the first and second test groups. In other words, the combination of CBT with tDCS and the combination of CBT with drug therapy led to a significant improvement in depression symptoms; however, no significant difference was reported between the effectiveness of these two combined interventions. Furthermore, the results of the follow-up test demonstrated that depression scores in both the post-test and follow-up phases significantly differed from the pre-test phase, indicating the durability of the applied interventions. Nevertheless, there was no significant difference in depression scores between the three groups during the three stages.

Table 2. Demographic indicators by three research groups

Variable (n=45)		Mean ± standard deviation/frequency (percentage)			Sig.
		first group	second group	third group	
Marital status	Married	9 (60)	11 (73)	7 (47)	0.18
	Single	6 (40)	4 (27)	8 (53)	
gender	Female	6 (40)	6 (40)	8 (53)	0.45
	Male	9 (60)	9 (60)	7 (47)	
Age (years)		33.93 ± 7.15	34.60 ± 8.87	33.80 ± 9.75	0.96

Table 3. Descriptive indices of research variables and mixed variance analysis results

Variable (n=45)		Mean ± standard deviation			Effects		
		Pre-test	post-test	follow-up	time	group	time*group
Working depression	1th group	22.66±7.73	17.80±5.38	16.53±7.09	$F_{(1,135)} = 9.90$ P=.002	$F_{(2,135)} = 3.83$ P=.024	$F_{(2,135)} = 1.16$ P=.314
	2th group	19.80±6.83	15.86±3.81	13.40±5.70			
	Control	26.13±9.81	25.00±7.82	24.66±9.91			
Work engagem.	1th group	79.26±10.17	97.33±10.59	89.66±14.45	$F_{(1,135)} = 23.38$ P=.001	$F_{(2,135)} = 4.17$ P=.042	$F_{(2,135)} = 1.21$ P=.301
	2th group	81.86±8.04	101.40±9.73	99.00±7.08			
	Control	86.60±10.75	89.80±14.05	86.40±14.81			

Table 3 presents the descriptive statistics (mean and standard deviation) for two variables working depression and work engagement across three time points (pre-test, post-test, and follow-up) for three groups. The results also include F values for time, group, and their interaction, showing significant differences over time and between groups, particularly for working depression (P = .002) and work engagement (P = .001).

Regarding cognitive flexibility and inhibition, the results indicated that for both variables, the effect of time and group was not significant, and the interaction effect of time and group was not significant. In other words, at least two groups had significant differences from each other. The follow-up test results suggested that only the first test group receiving CBT with tDCS significantly differed from the control group. Furthermore, the comparison of the three stages of pre-test, post-test, and follow-up using the follow-up test demonstrated that only the pre-test and post-test were significantly different from each other. These results did not persist until the follow-up stage. In addition, it can be stated that the three groups have gone through a different process over time.

5. Discussion

The results of the present study, which was conducted on 45 subjects (in the form of three groups of 15, including two experimental groups and one control group), pointed out that both combined interventions of CBT along with tDCS and drug therapy improved the symptoms of post-stroke depression. The brain was affected by the interventions, and these effects lasted for three months after the interventions. These findings are consistent with the results reported by Hasan et al. (18), who investigated the impact of tDCS over the DLPFC on the symptoms of post-stroke depression and central pain management in stroke patients. The results highlighted the effectiveness of the mentioned intervention in two disorders, and the six-month follow-up indicated the durability of the effect of electrical stimulation of the mentioned brain area on mood improvement and complete removal of pain. In addition, the results of the current research are in line with the report of Bucur and Papagno (17), who examined the research conducted in the field of treatment of tDCS and repeated magnetic stimulation of the brain for post-stroke depression. The results indicated that the effectiveness of these interventions was not sufficient to introduce them as independent methods. The current study, which used a combination of CBT and tDCS, pointed to the therapeutic adequacy of this combined intervention.

In explaining the findings of the current research in the framework of cognitive theory, it can be stated that this approach focuses more on people's beliefs than their behavior (35). In this view, depression is caused by a systematic negative bias in thinking processes, while emotional, behavioral, and physical symptoms are considered to be caused by cognitive abnormalities. In general, it can be argued that in this perspective, depressed patients think clinically differently from normal people. The cognitive approach also assumes that changes in thinking occur prior to the onset of a depressed mood. Therefore, cognitive behavioral psychotherapy tries to correct thinking and beliefs. The cognitive behavioral psychotherapy protocol used in the current study, which was specifically designed for patients with chronic mood complaints after stroke, included 12 individual treatment sessions. In the first three sessions, the psychologist established a relationship with the patient and created a safe space by trying to experience the world from the patient's point of view without judgment or criticism. In the subsequent two sessions, which was the goal-setting phase, activity cards (including pictures of a wide range of daily tasks, including leisure, sports, and life activities) were used, and concrete examples were given to stroke patients to help them choose personal goals. During these sessions, individual's beliefs regarding goal setting were examined and modified. In the next stage, which consisted of two sessions, cognitive behavioral therapy was used to help the

patient recognize the thoughts that cause negative mood and negative behavior. In these sessions, the psychologist used plans to explain negative and positive cognitions and prepare and record assignments. First, the psychologist described a "three-step sequence" of events, the events that lead to feelings and behavior. The patient was taught that events produce emotions, which in turn influence behavior. The patient was then encouraged to think of specific events in their daily life that led to negative emotions and subsequent behavior. Once he understood this sequence of events, a fourth step (the hidden part) was added to the explanatory scheme. With special attention to sequence, events unfold. Once the patient is introduced to this technique, the psychologist explains that hidden cognitions may have a negative or positive effect on feelings and behavior. In the last phase, which consists of three sessions, the patient was taught to challenge specific negative and irrational thoughts and transform these thoughts into logical "helpful" thoughts. The patient and the psychologist analyzed the concrete examples of the four-step sequences together, and the patient was assigned homework. In general, during the implementation of this protocol, the patient's irrational thoughts and beliefs were modified and replaced with efficient beliefs, and the changes in depressed mood were visible in most subjects in the final sessions. In general, cognitive behavioral psychotherapy brings about positive changes in the mood of patients through improvement and correction of false beliefs, and the use of drug therapy and tDCS in the two test groups caused more marked effects.

In order to explain the findings of the research regarding the effects of drug therapy in the framework of the cognitive neuropsychological model, it can be stated that according to this theory, in order for the primary biological effects of drug therapy to turn into clinical improvement, a positive change must occur in the processing of emotionally salient information. Studies have designated that such a change in behavioral and neurological levels occurs even after taking a single dose of an antidepressant (36). Subsequently, this newer positive bias will be reinforced in interaction with the social environment and will lead to more positive interactions, the continuation of biological and neuro-adaptive processes, and the formation of a beneficial cycle. In fact, it can be argued that the theory of cognitive neuropsychology states that drug therapy leads to mood improvement through changes in the processing of emotional information. As mentioned earlier, cognitive behavioral psychotherapy leads to mood improvement through modifying beliefs. Therefore, it can be stated that the improvement of information processing that occurs through drug therapy can provide the basis for correcting and changing beliefs, and therefore, these two interventions can have a valuable synergy to improve mood in people with depressive symptoms.

Furthermore, in order to explain the research findings regarding the effects of tDCS, it can be considered that studies have suggested that new therapeutic approaches that apply a magnetic or electric current through the scalp exert a neuromodulating effect on the brain. For instance, direct current transcranial stimulation has a positive impact on improving emotional processing (37). In healthy people, brain stimulation modulates neural activity in the underlying circuits of emotion processing. After a session of electrical stimulation, the processing of emotional faces and emotional memory significantly improves (38). It seems that similar to drug therapy, tDCS, which enhances emotional processing, has a significant effect on improving mood in people with depression, and there is a beneficial synergy of combining tDCS with cognitive behavioral psychotherapy in reducing depression symptoms. In addition, it seems that the use of cognitive behavioral psychotherapy targets and modifies the content of beliefs, while drug interventions along with tDCS improve and modify the belief processing process.

Regarding the investigated cognitive functions, the difference between the interventions of the first group in the first and second experiments lies in the use of tDCS in the first group and drug therapy in the second group, and only the interventions of the first group lead to significant changes in the cognitive functions of working memory. It seems that the tDCS over DLPFC has led to the improvement of the mentioned executive functions, and drug treatment with citalopram had no effect on the improvement of cognitive functions. According to these results, it is hypothesized that tDCS may lead to the improvement of depression symptoms through the improvement of cognitive functions, and there is a need for more studies in this field.

6. Conclusion

The present study sought to compare the effect of cognitive behavioral therapy combined with transcranial direct current stimulation (the first experimental group) or pharmacotherapy with citalopram (the second experimental group) on the improvement of depression symptoms and working memory of stroke patients. In summary, it can be concluded that the intervention of the first group had a long-term effect on improving depression symptoms and a short-term effect on improving cognitive function and working memory. In addition, the intervention of the second group had a long-term impact on the improvement of depression symptoms in stroke patients and did not have a significant effect on the improvement of the

aforementioned cognitive functions.

It is suggested to conduct a similar study by controlling the variables of gender and the location of the stroke in the brain, dividing the sample group into more subgroups, and comparing the interventions in a combined and separate manner so that the effects of each intervention individually and in combination with other interventions are apparent. Furthermore, the use of brain imaging methods can help clarify the therapeutic effects of employed interventions.

Acknowledgments

Hereby, we express our gratitude to Dr. Hashem Zahi, a neurologist, and his clinic staff, as well as all the participants and their guardians who provided the basis for the implementation of this research.

Conflicts of interest

The authors declare that they have no conflict of interest.

References

1. Feigin VL, Brainin M, Norrving B, Martins S, Sacco RL, Hacke W, et al. World Stroke Organization (WSO): global stroke fact sheet 2022. International Journal of Stroke. 2022;17(1):18-29.
2. Zhao Y, Zhang X, Chen X, Wei Y. Neuronal injuries in cerebral infarction and ischemic stroke: From mechanisms to treatment. International Journal of Molecular Medicine. 2022;49(2):1-9.
3. Medeiros GC, Roy D, Kontos N, Beach SR. Post-stroke depression: a 2020 updated review. General hospital psychiatry. 2020;66:70-80.
4. Rost NS, Brodtmann A, Pase MP, van Veluw SJ, Biffi A, Duering M, et al. Post-stroke cognitive impairment and dementia. Circulation Research. 2022;130(8):1252-71.
5. Robinson RG, Jorge RE. Post-stroke depression: a review. American Journal of Psychiatry. 2016;173(3):221-31.
6. Gonzalez J, Morales IS, Villarreal DM, Derrick BE. Low-frequency stimulation induces long-term depression and slow onset long-term potentiation at perforant path-dentate gyrus synapses in vivo. Journal of neurophysiology. 2014;111(6):1259-73.
7. Tu J, Wang L-X, Wen H-F, Xu Y-C, Wang P-F. The association of different types of cerebral infarction with post-stroke depression and cognitive impairment. Medicine. 2018;97(23).
8. Villa RF, Ferrari F, Moretti A. Post-stroke depression: mechanisms and pharmacological treatment. Pharmacology & therapeutics. 2018;184:131-44.
9. Alavian F, Haizadeh S. Cognitive disorders resulting from stroke. Advances in Cognitive Sciences. 2018;20(3):15-33.
10. Reichenberg A. The assessment of neuropsychological functioning in schizophrenia. Dialogues in clinical neuroscience. 2010;12(3):383-92.
11. Beloe P, Derakshan N. Adaptive working memory training can reduce anxiety and depression vulnerability in adolescents. Developmental science. 2020;23(4):e12831.
12. Baddeley AD, Hitch GJ. Working memory (Vol. 8). New York: GA Bower (ed), Recent advances in learning and motivation. 1974.
13. Starkstein SE, Hayhow BD. Treatment of post-stroke depression. Current treatment options in neurology. 2019;21:1-10.
14. Wang S-B, Wang Y-Y, Zhang Q-E, Wu S-L, Ng CH, Ungvari GS, et al. Cognitive behavioral therapy for post-stroke depression: a meta-analysis. Journal of affective disorders. 2018;235:589-96.
15. Withers H, Plumbley-Jones J, Pyatt E, Williams L, Yule L, Kyte D. The effectiveness of cognitive behavioural therapy versus antidepressants for treatment of post-stroke depression in adults. The British Student Doctor Journal. 2021;5(1):5-17.
16. Zhang C, He L, Li Z, Qiu H, Wang X, Zhang Y. Effectiveness of non-pharmacological interventions for treating post-stroke depression: Study protocol of an umbrella review of systematic reviews and meta-analyses. Medicine. 2021;100(51).
17. Bucur M, Papagno C. A systematic review of noninvasive brain stimulation for post-stroke depression. Journal of affective disorders. 2018;238:69-78.
18. Hassan AB, Danazumi MS, Abdullahi A, Yakasai AM. Effect of transcranial direct current stimulation (tDCS) delivered via dorsolateral prefrontal cortex on central post-stroke pain and depression: a case report. Physiotherapy Theory and Practice. 2022;38(11):1799-806.
19. Rigi Kooteh B, Mahdavi A, Rigi A, Borhani T, Hashemzahi Z, Seyednejad M, Sarani yaztappeh J. The Effectiveness of Transcranial Direct Current Electrical Stimulation on Reducing Craving: a Meta-Analytic Study. The Neuroscience Journal of Shefaye Khatam. 2021;10(1):99-110.
20. Yamada Y, Sumiyoshi T. Neurobiological mechanisms of transcranial direct current stimulation for psychiatric disorders; neurophysiological, chemical, and anatomical considerations. Frontiers in human neuroscience. 2021;15:631838.
21. Koops S, Blom JD, Bouachmir O, Slot MI, Neggers B, Sommer IE. Treating auditory hallucinations with transcranial direct current stimulation in a double-blind, randomized trial. Schizophrenia research. 2018;201:329-36.
22. Sudbrack-Oliveira P, Razza LB, Brunoni AR. Noninvasive cortical stimulation: Transcranial direct current stimulation (tDCS). International Review of Neurobiology. 2021;159:1-22.
23. Chan MM, Yau SS, Han YM. The neurobiology of prefrontal transcranial direct current stimulation (tDCS) in promoting brain plasticity: A systematic review and meta-analyses of human and rodent studies. Neuroscience & Biobehavioral Reviews. 2021;125:392-416.
24. Oldrati V, Schutter DJ. Targeting the human cerebellum with transcranial direct current stimulation to modulate behavior: a meta-analysis. The Cerebellum. 2018;17:228-36.
25. Martin D, Teng J, Lo T, Alonzo A, Goh T, Iacoviello B, et al. Clinical pilot study of transcranial direct current stimulation combined with Cognitive Emotional Training for medication resistant depression. Journal of affective disorders. 2018;232:89-95.
26. Brunoni AR, Nitsche MA, Bolognini N, Bikson M, Wagner T, Merabet L, et al. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. Brain stimulation. 2012;5(3):175-95.
27. Utz KS, Dimova V, Oppenländer K, Kerkhoff G. Electrified minds: transcranial direct current stimulation (tDCS) and galvanic vestibular stimulation (GVS) as methods of noninvasive brain stimulation in neuropsychology—a review of current data and future implications. Neuropsychologia. 2010;48(10):2789-810.
28. Nikolin S, Tan YY, Schwaab A, Moffa A, Loo CK, Martin D. An investigation of working memory deficits in depression using the n-back task: A systematic review and meta-analysis. Journal of Affective Disorders. 2021;284:1-8.
29. Sisay T, Mulate M, Hailu T, Belete TM. The prevalence of depression and anxiety among cardiovascular patients at University of Gondar specialized hospital using beck's depression inventory II and beck anxiety inventory: A cross-sectional study. Heliyon. 2024;10(2).
30. Segal DL, Coolidge FL, Cahill BS, O'Riley AA. Psychometric properties of the Beck Depression Inventory—II (BDI-II) among community-dwelling older adults. Behavior modification. 2008;32(1):3-20.
31. Rahimi C. Application of Beck-2 depression questionnaire in Iranian students. Clinical Psychology and Personality

2013;21(10):173-88.
32. Li H, Zhu N, Klomparens EA, Xu S, Wang M, Wang Q, et al. Application of functional near-infrared spectroscopy to explore the neural mechanism of transcranial direct current stimulation for post-stroke depression. Neurological Research. 2019;41(8):714-21.
33. Kootker JA, Rasquin SM, Smits P, Geurts AC, van Heugten CM, Fasotti L. An augmented cognitive behavioural therapy for treating post-stroke depression: description of a treatment protocol. Clinical rehabilitation. 2015;29(9):833-43.
34. Goerigk SA, Padberg F, Chekroud A, Kambeitz J, Bühner M, Brunoni AR. Parsing the antidepressant effects of noninvasive brain stimulation and pharmacotherapy: A symptom clustering approach on ELECT-TDCS. Brain Stimulation. 2021;14(4):906-12.
35. LeMoult J, Gotlib IH. Depression: A cognitive perspective. Clinical psychology review. 2019;69:51-66.
36. Godlewska BR, Harmer CJ. Cognitive neuropsychological theory of antidepressant action: a modern-day approach to depression and its treatment. Psychopharmacology. 2021;238(5):1265-78.
37. Shiozawa P, Fregni F, Benseñor IM, Lotufo PA, Berlim MT, Daskalakis JZ, et al. Transcranial direct current stimulation for major depression: an updated systematic review and meta-analysis. International Journal of Neuropsychopharmacology. 2014;17(9):1443-52.
38. De Raedt R, Leyman L, Baeken C, Van Schuerbeek P, Luypaert R, Vanderhasselt M-A, Dannlowski U. Neurocognitive effects of HF-rTMS over the dorsolateral prefrontal cortex on the attentional processing of emotional information in healthy women: an event-related fMRI study. Biological psychology. 2010;85(3):487-95.