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Meta-analysis of the Effectiveness of Transcranial Direct Current Stimulation (tDCS) on Neurocognitive Function in People with Mild Neurocognitive Impairment

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Abstract

Objective: The aim of the present study was investigating the effectiveness of Transcranial Direct Current Stimulation (tDCS) on neurocognitive performance in people with mild neurocognitive impairment. Using meta-analysis and integrating the research results, this study has specified the extent of the effect of Transcranial Direct Current Stimulation on improvement of neurocognitive function in people with mild neurocognitive impairment.

Method: For meta-analyses Magiran, SID, and Irandoc databases were used to search Persian articles and Science direct, Scopus, and PubMed databases were used to find foreign articles, using 'MCI', 'transcranial direct current stimulation', tDCS, and 'mild cognitive impairment' key words for foreign articles and their Persian equivalents for Persian articles. Of the 29 studies, 11 that were methodologically acceptable were meta-analyzed. The research tool was a meta-analysis checklist.

Results: The results of meta-analysis indicated publication bias in the studies. Due to the heterogeneity of the studies, a random effect model was used. The effect of Hedges for the impact of Transcranial Direct Current Stimulation on neurocognitive functions in people with mild neurocognitive impairment was 0.26, which is a large effect.

Conclusion: This result shows clinicians can choose transcranial direct current stimulation (tDCS) as effective intervention for patients who suffer from mild cognitive impairments. More investigations are necessary to find the cognitive benefits of using transcranial direct current stimulation in elderly people and other cognitive impaired persons.

Key words: Trans Cranial Direct Current Stimulation, Neurocognitive domains, Mild Cognitive Impairment (MCI), Meta-Analysis, Aging health.

Introduction

Increasing longevity and life expectancy along with the rapid growth of old population in developing and developed countries have changed the face of the world and has confronted human societies with the phenomenon of aging (Nikogftar & Saeedi, 2012). Aging, as one of the periods of human development, is usually defined based on age, and the most common scale is chronological age, which in Western countries the traditional option of aging is 60-65 years old (Rowshan, 2015).

Aging is a dynamic, natural, and growing process, in which elderly are vulnerable to some difficulties and disorders such as distress, lack of life expectancy, depression, problems of physical activities, and the like, due to some issues in this period of life, such as getting retired and feeling lonely and exclusion. So, it is important to find ways to decrease these problems in this period of life (Ghasemi Pirbalouti, Shariat, & Ghazanfari, 2019).

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With this description, aging health should be considered important by planners in this field. Health psychology is a new and rapidly developing field that can be defined as the application of psychological methods to study behaviors related to health, disease, and health care. Health psychology focuses on health promotion and disease prevention and treatment. Health psychologists also look at how people react, cope with illness, and recover the illness (Saffarinia, 2014).

Healthy aging is linked with a variety of changes in cerebral cortex function, such as decreased regional function and increased neural activities. These physiological differences, when cognitive ability is preserved, are often defined as successful adaptation, while these cognitive functions are often no longer preserved in aging. Mild Cognitive Impairment (MCI), for example, is one of the aging pathologies in which people show decline in cognitive functions compared to normal age period (Emonson, Fitzgerald, Rogasch, & Hoy, 2019). Cognitive impairment affects daily life and professional and social interaction. Attention to cognitive and neurocognitive interventions have increased due to the limitations of drug therapies (Alipour, Javanmard, Garegozlo, 2019) so psychologist (neuropsychologists, cognitive psychologist, clinical psychologist and etc.) should note to this subject to improve quality of life for these impaired people.

According to the American Psychiatric Association (APA) in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (2013), NCDs include the variety of disorders in which there are main clinical deficiencies in cognitive function that are acquired gradually. Although there are cognitive deficits in many mental disorders (such as schizophrenia and bipolar disorders), only those disorders whose main features are cognitive fall into the NCD group. The NCDs are disorders which are not present from birth or childhood, and are as the result of reduction in previous levels of functions and, according to APA, are unique syndromes in DSM-5 categories (American psychiatric association, 2013). A clinical diagnosis of MCI is made by a patient care giver's history on the patient's behavior and neuropsychological examinations such as Mini-Mental State Examination (MMSE) (Yoo & Hong, 2019).

Cognitive domains from the DSM-5 perspective include six major sub-disciplines and their subsets:

Complex attention: sustained attention, divided attention, selective attention, processing speed,

executive function: planning, decision making, working memory, responding to feedback/error correction, overriding habits/inhibition, mental flexibility,

learning and memory: immediate memory, recent memory (including free recall, and recognition memory), very-long-term memory (semantic, autobiographical), implicit learning,

language: expressive language [(e.g. naming, word finding, fluency, grammar, and syntax), receptive language,

perceptual-motor: abilities incorporated under the terms of visual perception, visual-constructional, perceptual-motor, paraxis and gnosis,

social cognition: recognition of emotions, theory of mind.

Peterson et al. applied the term "Mild Cognitive Impairment" (MCI) to describe a period in the longitudinal course of neurological disease in which cognition is not normal in respect to age expectations, but in cases where daily functioning is not disturbed enough to be able to diagnose dementia. In most people, MCI constitutes that level of cognitive function wherein low-functioning of normal older persons and high functioning of dementia patients cannot be reliably diagnosed. If individuals who are labeled as MCI are regarded as normal people, or belonging to population susceptible to dementia, then we can consider it as uncertainty of clinician rather than a "condition" present in the patient. As the group from which the person came is uncertain, the clinician attributes it to MCI. As it is identified, this state of uncertainty can be considered as a risk factor for the patient due to the consequent development of dementia (Smith & Bondi, 2013).

Non-invasive brain stimulation is a versatile tool to modulate psychological processes via alterations of brain activity, and excitability. tDCS is a non-invasive method that allows reverse modulation of activity in specific areas of the brain that creates brain-behavior links in a range of cognitive, motor, social, and emotional domains. In addition, it was shown to be effective in modifying behavior, accelerating learning, and promoting task performance temporarily in healthy people (Thair, Holloway, Newport & Smith, 2017; Nissim et al., 2019).

Today, the tendency to use Transcranial direct current stimulation (tDCS), as a modern and advanced, safe and cost-effective approach to improve cognitive activity and reduce mental disorders, has increased significantly. The underlying mechanism(s) of action of tDCS and its effects on brain function are not yet fully understood. This is a method in which a weak direct current (1 to 4 mA) is applied to the scalp, which causes long-term changes in the polarity of the cerebral cortex following the depolarization and hyperpolarization of neurons and the effect on nerve receptors. In other words, in this type of electrical stimulation, some points of the head are targeted using weak electric currents. Transcranial direct current stimulation alters the impulsiveness of neurons in the specified area of the brain, regulates the neural network activity, and modifies the activity of stimulated brain neurons. Researchers believe that this stimulation is effective in improving organs and reducing many disorders and mental injuries. Bogio et al. believe that one of the most important characteristics of transcranial direct current stimulation is its ability to make cortical changes, even after the end of stimulation. They have found that after 5 sessions of direct current stimulation at 1 mA of anode 20, this stimulation will have beneficial effects in improving psychotic disorders (Oraki & Shahmoradi, 2018; Yong, A'guid, Nitsche, 2015).

One of the studies done on the effectiveness of transcranial direct current stimulation on neurocognitive functions in people with mild neurocognitive impairment includes Murugaraja et al.'s (2017) study that investigated the feasibility, tolerability, and clinical utility of tDCS in patients with MCI. In this study, the researchers administered tDCS with the intensity of 2 mA and 20 minutes' duration per day for five successive days with anode over left dorsolateral prefrontal cortex (DLPFC) and cathode over right supra orbital region on 11 patients with MCI. The intervention result was measured immediately and one month after the 5th intervention session through picture memory impairment test (PMIT). The results of examination showed that all participants tolerated tDCS treatment without any significant alternative effects. It was also shown that stimulation of left DLPFC with tDCS significantly improved the immediate and delayed patient's recall performance in PMIT after 5 days' stimulation, whose effectiveness was constant at least after one month follow up. Murugaraja et al.'s study supporters that tDCS is a safe and potentially beneficial in removing cognitive deficits in patients with MCI and provides a model for more studies with randomized and control group.

Another study was done by Emonson et al. (2019) aiming at determining the neurobiological effects of tDCS in younger adults, older adults, and adults with MCI and its relationship with their cognitive performance. The participants consisted of 20 healthy younger adults, 20 healthy older adults and 9 patients with MCI who were administered neuropsychological tasks and TMSEEG before and after 20 minutes anodal tDCS to the left dorsolateral prefrontal cortex (DLPFC). Also, EEG was recorded during 2-Back working memory task. Younger adults showed changes in early TMS-Evoked Potentials (TEPs) after administering tDCS, but both younger and older adults showed adverse relationship with cognitive performance after stimulation. However, the treatment group, i.e. MCI group, showed no change in TEPs or ERPs over time. The result of comparing two groups showed significant difference in the changes occurred in amplitude of early TEP (P60) and ERP (N100) peaks of younger and older adults. Their finding indicated that tDCS was effective in modulating cortical activity in younger and older healthy adults in various ways. The results of this study suggest that different factors such as age and the presence or absence of cognitive impairment can be related to different responses to tDCS, so these factors should be considered in conducting studies on the effectiveness of tDCS on healthy and pathological elderly.

In a similar study, Fileccia et al. (2019) investigated the effectiveness of 20-day anodal tDCS on the cognitive behavior of 17 patients with MCI in comparison with 17 individuals with matched MCI. Initially, participants were administered neuropsychological examination and then were assigned to two anodal or sham groups randomly. The groups received 20-minute tDCS treatment sessions for 20 days (five days per week) according tDCS standard protocol and giving 2-mAanodal stimulation over the left dorsolateral prefrontal cortex (DLPFC). After conducting the last stimulation in the last day, the second neuropsychological evaluation was conducted. Then the researchers compared the pre and post stimulation results in both groups using ANONA statistical analysis. The result of exposing patients to anodal stimulation in follow up stage and figure naming test in a general index of cognitive function (Brief Mental Deterioration Battery test) as well as mood measurement test (Beck Depression Inventory), indicated improved episodic verbal memory in patients. The results suggest that Anodal tDCS could be effective in improvement of cognitive performance.

In another similar study, Meinzer et al. (2015) in their study on the effectiveness of tDCSb on the cognitive behavior of patients with MCI and administering anodal-tDCS to the left inferior frontal cortex of patients with MCI during task-related and resting-state functional magnetic resonance imaging (fMRI), evaluated its impact on cognitive performance and brain function of these patients. The patients produced fewer correct semantic-word-retrieval responses during sham stimulation compared to control group. The result showed that Anodal-tDCS significantly affected performance to the level of controls, decreased task-related prefrontal hyperactivity, and led to "normalization" of abnormal network configuration during resting-state fMRI.

Method

Given that the purpose of this study was to describe, analyze and integrate the results of related studies on the efficacy of cognitive rehabilitation for the elderly with mild neurocognitive impairment based on previous research, meta-analysis was used to analyze data. Meta-analysis research is applied in type which is categorized in qualitative studies.

Participants and procedure

In this study, the focus was on some research on a specific topic. So, the research population in this study was the conducted theses and articles related to the efficacy of cognitive rehabilitation for the elderly with mild neurocognitive impairment. This population, more specifically, consisted of the dissertations of some universities, published articles in valid journals and publications available in a number of reliable and well-known academic databases.

As this study was not based on sampling and the researcher attempted to examine the whole population, the researcher's focus was on studying and collecting the data required to summarize and draw appropriate conclusions from the whole population. To search Persian articles, the Irandoc, magiran, and SID databases were used, and for foreign articles, Sciencedirect ،Scopus, and PubMed websites were searched, using MCI, transcranial direct current stimulation, tDCS, and mild cognitive impairment keywords for English databases and their Persian equivalents for Persian websites. The inclusion criteria in this meta-analysis study were: 1) tDCS intervention in mild neurocognitive disorder, 2) Having the necessary conditions in terms of methodology (hypothesis making, research method, population, sample, statistical analysis method and correctness of calculations, 3) Research should not be based on a specific neurocognitive disorder (such as Alzheimer’s, etc.) and mild neurocognitive disorder (MCI) should be considered in general. Out of about 1200 reviewed articles between 2004-2019, 29 were collected with completely matching topics or relatively high thematic similarity and suitable for meta-analysis, then, by observing inclusion criteria of each study for meta-analysis, 11 eligible studies were identified and meta-analysis were performed on them.

Ethical statement

According to the method of this research, which is meta-analysis, the researcher attempted to find all previous research on the subject. The mentioned databases have been studied very carefully; however, it should be noted that due to the multiplicity of neurocognitive fields and changes in the subject of neurocognitive disorders, some research might have been missed in the search engine.

Instruments

Library method was used to collect data. Descriptive statistics indicators have been used to describe the data obtained from the statistical sample, which were analyzed using SPSS 22 software. Also, meta-analytical analyzes were used to examine the research question. In this study, meta-analysis models of fixed effects and random effects were used to analyze data and to obtain the size of the dissociative and general effect for studies, *g* hedges effect; to investigate the distribution bias, funnel plots and correction test and Duval-tweed fitting; to investigate the number of missing studies, the error-free N-test; to investigate the heterogeneity of the studies, Q and I^2 tests; and to combine the probabilities, the Weiner t-method were used. Using the effect size combination method, all these analyses were performed using Excel software and editing comprehensive meta-analysis software 2 (CMA2).

Findings

Research has shown that regarding the effectiveness of transcranial direct current stimulation (tDCS) intervention on improving cognitive function in people with mild neurocognitive impairment, 53 factors have been identified in 11 studies, of which 16 factors have emphasized the absence of relationship and the rest have confirmed the presence of correlation. In fact, research null hypotheses have been rejected in 37 cases ($\chi2 = 0.284$) and the rest have been confirmed (Table 1).

Table 1. Descriptive statistics and Chi² calculation of research hypotheses

$^2\chi$	F_o - F_e	F_e	F_o	
0.284			37	H_0 rejected
0.049	3.33	5.67	16	H_0 confirmed
53 factors have been entered into the analysis				Total (53factors)

Is the significance of the research hypotheses of the studies meaningful?

Comparing Table 1 with Chi-square Distribution Table (Delaware, 2012), it is concluded that χ^2 of rejected hypotheses with a value of 0.049 is less than χ^2 of the Chi-square distribution, so H_0 is rejected and H_1 is confirmed at 0.05.

In this section, first the funnel diagram based on standard error and accuracy indices in each of the studies is presented in unmodified and modified form, and then the results of analysis and the effect size for each study are reported. Also the

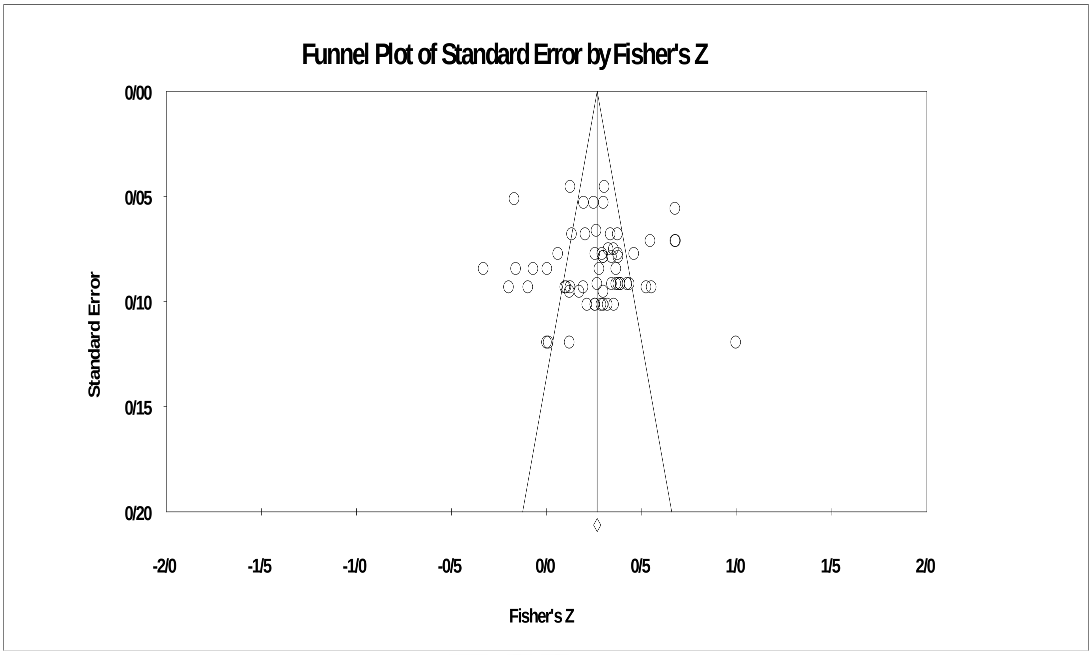

Figure 1. Funnel diagram based on standard error index of the studies

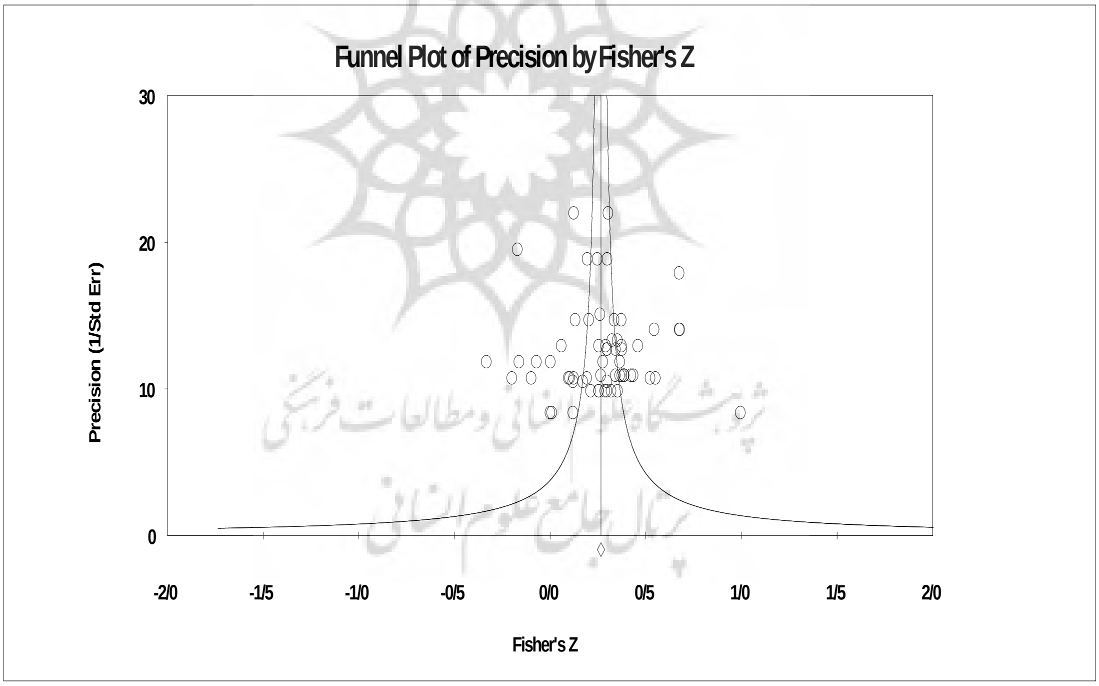

Figure 2. Funnel diagram based on accuracy index

homogeneity of studies was tested and the safe incomplete number for each study was determined. According to Figures 1 and 2, it can be seen that the studies used in this research are not symmetrically distributed around the mean of effect size and the scatter of studies around one side of the mean indicates the existence of bias in the studies. Large studies appear at the top of the chart and small studies appear at the bottom of the chart. In order to investigate and eliminate this bias, the Duval and Tweedie arrangement and completion method was used. This method calculates the missing studies on the left side

Table 2. Duval and Tweedie arrangement and completion method

	Added studies	Fixed effects			Random effects			Q value
		Estimation point	Low level	High level	Estimation point	Low level	High level	
observed values		0.21964	0.14160	0.20750	0.26070	0.20902	0.31093	315.78469
Modified values	8	0.16696	0.14985	0.20394	0.19569	0.13768	0.25237	562.45543

of the graph, creation of which eliminates the state of bias. Table 3 shows the results of using this method. Based on the results in Table 2, eight missing studies are included, and the amount of point estimation in the fixed effect model, using the Duval and Tweedie arrangement and completion method, has been changed from 0.21964 to 0.16696. Also, the point estimation in the random effect model has turned from 0.26070 to 0.19569. In other words, adding 8 studies to the left side of the effect size mean creates a state of symmetry in this graph.

According to Figures 3 and 4, by adding 8 studies to the left side of the mean, the existing bias was eliminated and the distribution of studies has been changed from asymmetric to symmetric. Added studies are displayed in black circles.

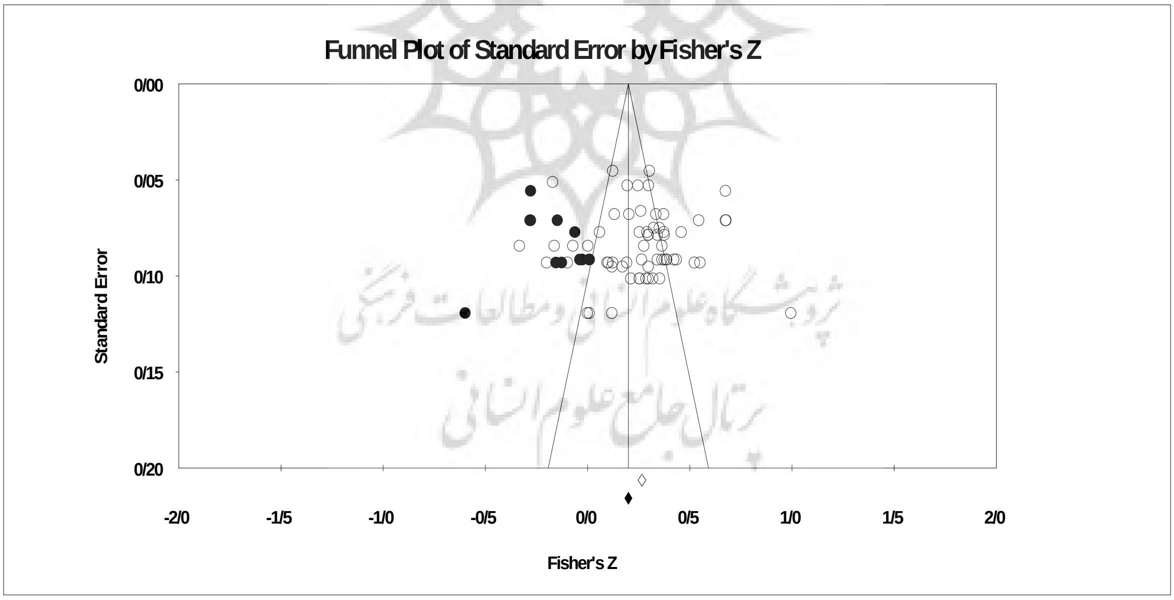

Figure 3. Modified funnel diagram based on the standard error index

Investigating the homogeneity of studies

Q test was used to evaluate the homogeneity of the studies. The results of this test are given in Table 3.

Table 3: homogeneity test results

Model	Q value	Df	P value	I^2
Fixed	90	21	0.0001	0.28470

As can be seen in Table 3, the value of Q is equal to 90, which is significant with a probability of less than 0.05. So the null hypothesis based on homogeneity of studies is rejected, which indicates that the studies

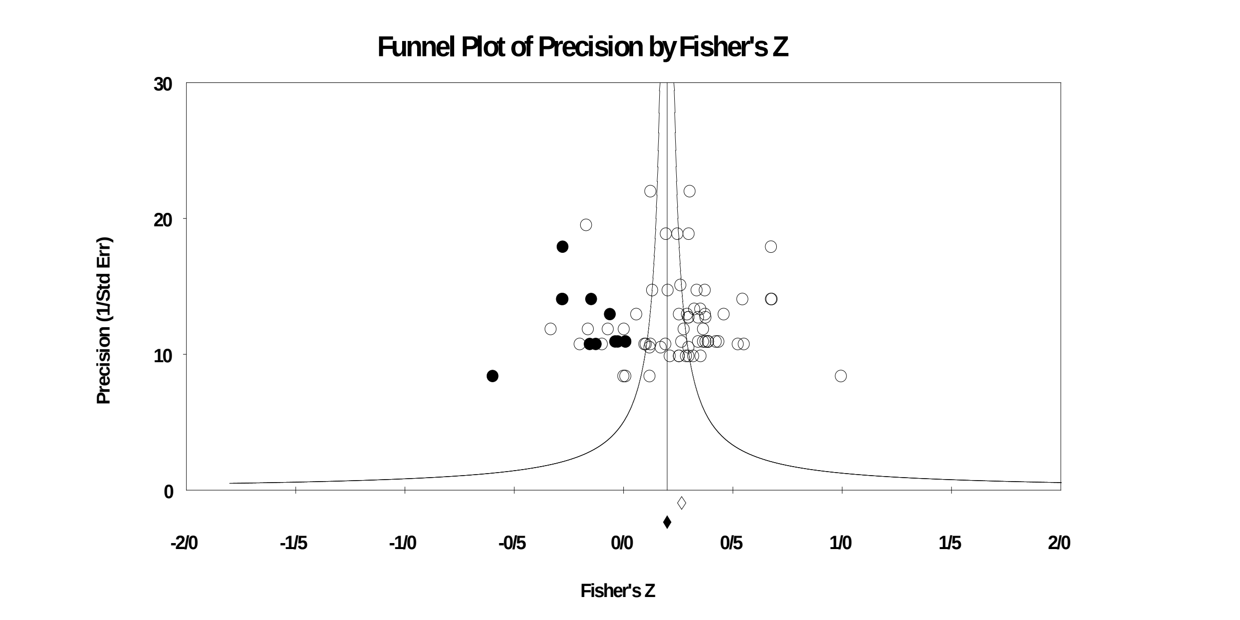

Figure 4. Modified funnel diagram based on accuracy index

under investigation are heterogeneous. Also, index I^2 shows that 0.28470% of the effect size changes in all studies are due to heterogeneity of studies.

To investigate the overall significance of the effect size after the integration of studies, two fixed and random models have been used, the results of which are shown in Table 4.

Table 4: Results of combining the effect size of studies and their significance

Model	Statistical indexes					Mean effects calculation	
	g hedges	Low level	High level	Z value	P value	+	-
Fixed	0.158	0.086	0.214	39.208	0.0001	0.287	o.168
Random	0.260	0.242	0.278	27.054	0.0001		

As can be seen in Table 4, the overall effect size for studies in the fixed effects model based on the Hedges g index is 0.158 with 95% confidence in the range of 0.086 to 0.214, and for the random effects model is 0.260 with 95% confidence in the range of 0.242 to 0.278.

Investigating the studies publication bias

In order to investigate and determine the bias of combined studies publication, the safe incomplete number index was used. Table 5 shows the results of publication bias.

The results of Table 5 show that 1408 missing studies with an effect size equal to zero are needed to turn the above significant result into a non-significant result and the obtained P value reach the alpha level.

Table 5 Results of study publication bias

Z value of observed studies	P value	Alpha value	Z Alpha	Observed studies	Missing studies
26.39193	0.0001	0.05000	1.95996	29	1408

In the review of research in the area of the research question of whether Transcranial direct current stimulation (tDCS) intervention improve neurocognitive functions in people with mild neurocognitive impairment, there were 53 factors in the statistical sample, of which influential and correlational variables include performance and completion time, selective attention, planning ability tasks, left DLPFC stimulation, tDCS, age, gender, anodal, state anxiety, duration of treatment, control level, and number of sessions. In analyzing the data to confirm or reject the research null hypotheses of studies under investigation, using the statistical index of chi-square, the calculated value was equal to 0.052, which as is less than the critical chi value (P> 0.05), it is significant.

Discussion and Conclusion

Research has shown that regarding the effectiveness of transcranial direct current stimulation (tDCS) intervention on improving cognitive function in people with mild neurological cognitive impairment, 53 factors have been identified in 11 studies, of which 16 factors emphasized the absence of the relationship and the rest confirmed the existence of the relationship. In fact, the research null hypotheses have been rejected in 37 cases (χ^2 equals 0.284) and the rest have been confirmed.

In the review of the previous studies to answer the research question of whether Transcranial direct current stimulation (tDCS) intervention improves neurocognitive functions in people with mild neurocognitive impairment, 53 factors were identified in the statistical sample, of which influential and correlational variables include performance and completion time, selective attention, planning ability tasks, left DLPFC stimulation, tDCS, age, gender, anodal, state anxiety, duration of treatment, control level, and number of sessions. In analyzing the data to confirm or reject the research null hypotheses of studies under investigation, using the statistical index of chi-square, the calculated value was equal to 0.052, which is significant at P> 0.05.

The results of the present study confirm the results of Gonzalez et al. (2018), Gomes et al. (2019), Filleccia et al. (2019), Berryhill et al. (2018), Yong et al. (2015), Liu et al. (2019), Langawa et al. (2018), Emonson et al. (2019), Das et al. (2018), Meinzer et al. (2015), Murugaraja et al. (20018), Yun et al. (2018), and Dan et al. (2017), and acknowledges that in these studies, the bias is much lower and the results are stronger.

It is suggested that future researchers categorize the factors identified in the present study and use new researcher-made tools to measure their quantity and correlation between different variables. Also, using TDCS along with other interventions can be more effective, which can be considered as a practical suggestion.

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