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A Systematic Review and Meta-analysis on the Effectiveness of Transcranial Direct Current Stimulation on Swallowing Function of Poststroke Patients

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Objective: The purpose of this study was to investigate the therapeutic effects of transcranial direct current stimulation on swallowing function in poststroke patients.

Design: We searched for potentially eligible randomized controlled trials from electronic databases, including the PubMed, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure, Wanfang, and Chinese Science and Technology Periodical (VIP) databases, from their inception to January 15, 2021. All statistical analyses were performed using RevMan 5.4, and the standardized mean difference with 95% confidence intervals was estimated for the swallowing function outcomes and to understand the mean effect size.

Results: Ten studies involving 343 participants were included in this meta-analysis. The overall analyses demonstrated a significant effect size for swallowing function. Subgroup analyses suggested that both acute and chronic stroke patients showed significant effects on swallowing function after transcranial direct current stimulation. Furthermore, compared with sham stimulation, transcranial direct current stimulation anodal to the affected, unaffected, and bilateral hemispheres can produce a significant effect size for swallowing function in stroke patients.

Conclusions: This meta-analysis showed that transcranial direct current stimulation is likely to be effective for the recovery of dysphagia in poststroke patients, in the acute or chronic phase, and that the effect of anodal transcranial direct current stimulation to unaffected hemispheres is larger.

Key Words: Dysphagia, Transcranial Direct Current Stimulation, Swallowing Function, Meta-analysis

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What Is Known

- Transcranial direct current stimulation (tDCS) is effective for the recovery of dysphagia in the acute and chronic stages after stroke.

What Is New

- When the unaffected hemisphere was anodized, the therapeutic effect of TDCS on the swallowing function after stroke was greater.

Dysphagia is a potentially fatal complication of stroke, and approximately 50% of poststroke patients experience swallowing disorders.[1,2] Prolonged swallowing problems in stroke patients are associated with high institutionalization rates, greater healthcare costs, poor outcomes, and many life-threatening complications, including dehydration, malnutrition, aspiration, respiratory infection, and death.[3,4] The development of effective interventions that can improve swallowing problems after stroke can not only help regain swallowing control but also reduce the complications of dysphagia.

Currently, traditional therapies include body position adjustment, diet adjustment, oral exercise training, swallowing training, acupuncture, and electrical stimulation, and their positive effects have been confirmed to some extent.[5,6] Over the past decade, noninvasive brain stimulation techniques, which regulate the excitability of the cerebral cortex, have been used to investigate the physiology and pathology of swallowing and as a therapeutic tool for improving swallowing function in the different poststroke stages.[2] As a noninvasive neuromodulatory approach, transcranial direct current stimulation (tDCS) is a promising treatment for poststroke swallowing function recovery, with many advantages over other stimulation procedures, including economic efficiency, feasibility, ease of administration, and portability.[7,8]

Ever since the first pilot study on the positive effect of tDCS combined with swallowing exercises in acute stroke patients with dysphagia was reported in 2011, there have been many large sample-size, well-designed randomized clinical trial (RCT) studies reporting its clinical effects.[9] Although most of these studies showed that tDCS had a beneficial effect on swallowing function in stroke patients,[9–15] one study showed that tDCS

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Dun-Bing Huang did the conceptualization, funding acquisition, project administration, and resources. Qian Lin and Xiao-Fei Jia did the data curation and formal analysis. Qian Lin did the investigation. Shu-Fang Lin and Xiao-Fei Jia did the methodology. Qian Lin and Shu-Fang Lin did the writing of the original draft. Xiao-Fei Jia and Dun-Bing Huang did the writing review and editing.

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had little effect on swallowing function,[16,17] and another showed that tDCS had no effect on the recovery of swallowing function.[18]

A recent systematic review evaluated the effectiveness of tDCS for poststroke dysphagia; however, some meaningful studies were not included in its meta-analyses, and further studies are needed to verify these results.[19] Therefore, we conducted this systematic review and meta-analysis to systematically synthesize evidence on the effectiveness of tDCS on swallowing function after stroke.

METHODS

We conducted this systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for RCTs[20] and registered our review protocol at the PROSPERO (https://www.crd.york.ac.uk/PROSPERO/, ID CRD42021232205). This study conforms to all Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and reports the required information accordingly (see Supplementary Checklist, Supplemental Digital Content 1, http://links.lww.com/PHM/B349).

Search Strategy

We searched for potentially eligible RCTs from electronic databases, including the PubMed, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure, Wanfang, and Chinese Science and Technology Periodical (VIP) databases, from their inception to January 15, 2021. The key words were "tDCS" or "transcranial direct current stimulation," "stroke," "post-stroke," "cerebrovascular disorders," or "cerebrovascular accident." The detailed search strategies for all the electronic database searches are listed in Supplemental Appendix S1 (Supplemental Digital Content 2, http://links.lww.com/PHM/B350; also available online at https://www.crd.york.ac.uk/PROSPERO/).

Eligibility Criteria

Two reviewers independently reviewed the abstracts of each article for the initial selection. To ensure the quality of the included literature, only articles that met the following inclusion criteria were retained for full-length text examination: (1) all of the participants were adults (≥18 yrs) and were diagnosed with ischemic or hemorrhagic stroke by computed tomography or magnetic resonance imaging; (2) the articles were focused on the effect of tDCS on the recovery of swallowing function; (3) the trials were RCTs with crossover and parallel designs; and (4) the outcome measures were standardized, validated dysphagia scales.

The exclusion criteria were as follows: (1) other study designs, such as reviews, meta-analyses, or case reports; (2) studies that were not published in English or Chinese; and (3) studies in which the required data were unavailable.

Any disagreement was settled by the two reviewers through discussion and negotiation.

Figure 1 is the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the study selection procedure.

Data Extraction

Two reviewers independently extracted data from the selected full-text studies using predefined data extraction sheets. The following data were extracted: study information (first author, publication year, country, sample size), patient characteristics (age, sex, stroke type), interventions (treatment, stimulation site, dosage, duration, concurrent exercises/therapy), and main outcome measure.

Assessment of Risk of Bias in Individual Studies

Two reviewers independently assessed the quality of the methodology of the extracted studies using the Cochrane Collaboration Risk of Bias Tool. Any disagreements were resolved through discussion and negotiation. The assessment contents included six aspects: selective bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. The overall judgment of each item for each study was categorized as "low," "high," and "unclear," according to the level of bias. Any disagreements were resolved through discussion and negotiation. In addition, we tested for publication bias using a simple funnel plot.

Statistical Analyses

All statistical analyses were performed using Reviewer Manager Software 5.4. A pooled estimate of the mean difference (MD) with the 95% confidence interval (CI) for continuous data from the same measure was calculated. If studies did not use the same measure for an outcome, then the standard MD (SMD) with the 95% CI was calculated instead. Heterogeneity among the included studies was assessed using the I^2 statistic, for which $P < 0.10$ and $I^2 > 50\%$ represented substantial heterogeneity. A random-effects model was used regardless of the level of heterogeneity.

RESULTS

Study Selection and Characteristics

The search identified a total of 1239 abstracts for screening and yielded 55 relevant studies for full-text review. After careful screening and assessment, 10 studies were finally included in the meta-analysis. The search results are shown in the flowchart in Figure 1, and detailed results are presented in Table 1. Of the 10 included RCTs, three were conducted in China, three in South Korea, and one each in the United States, Japan, Italy, and Germany. Three were published in English, and seven were published in Chinese. The included trials were conducted from 2011 to 2020. The eligible cases in the included studies totaled 343 patients: 187 in the experimental group and 156 in the control group. The groups consisted of 169 men and 114 women with an average age of 62.27 ± 3.17 yrs (1 study had incomplete data). The distribution of the stroke types was as follows: 73 subjects had acute stroke and 270 had chronic stroke. The outcome measures used in the literature in this study were different. Five RCTs included in this meta-analysis used the Dysphagia Outcome and Severity Scale (DOSS)[21] as the outcome measure. Two studies used the Functional Dysphagia Scale[22] as their outcome measure. The remaining three studies used the Fiberoptic Endoscopic Dysphagia Severity Scale,[23] the modified Mann Assessment of Swallowing Ability,[24] and the Kubota Water Swallowing Test.[25] If possible, we extracted DOSS data as the main outcome indicator because this scale was the most frequently used in this particular group of

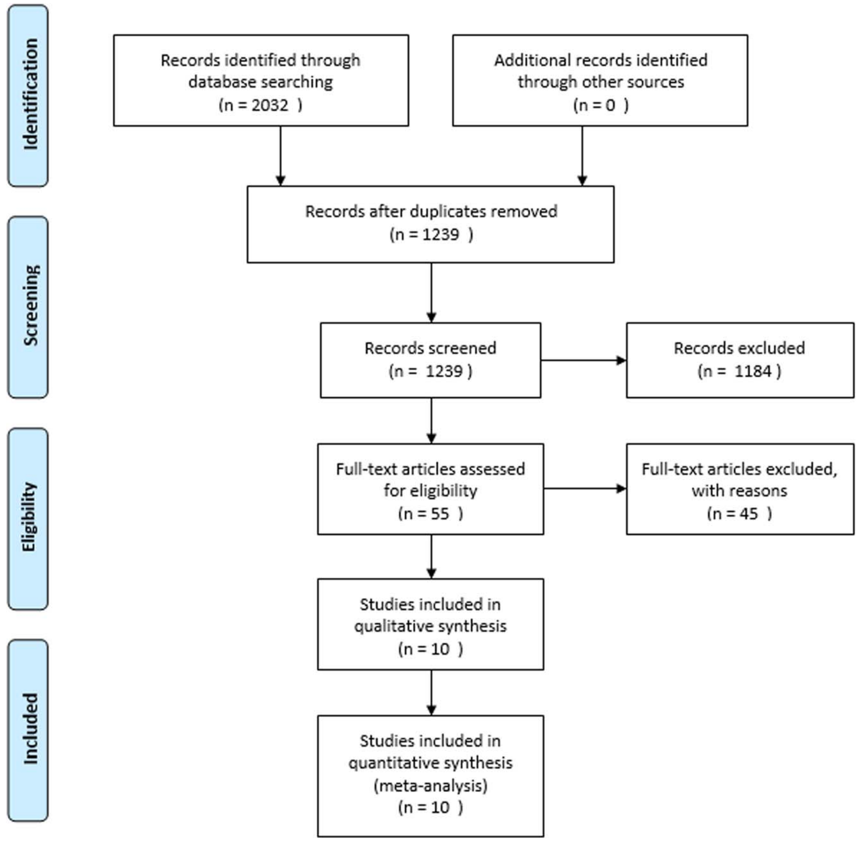

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the study selection procedure.

trials. Otherwise, we evaluated the severity of dysphagia instead of measuring feeding status. Because of the different scales included in the analysis, the directionality of the scales was different. We defined a greater number as indicating positive improvement, but in the inverse situation (greater number meaning decline), we multiplied the effect size by −1 to orient the scales of all the trials in the same direction.

Results of the Meta-analysis

Risk of Bias Within the Studies

Figure 2 shows a summary of the risk of bias of the included studies. All the included trials reported randomized allocation, but only four of them described the method of the randomization sequence generation.[13–16] Two studies clearly reported allocation concealment.[13,16] Six studies pointed out that the single-blind method was used,[9,11,13,16,18] and five of them pointed out that blinding was used for outcome assessment.[11,13,16,18] The risk of attrition bias was low in six studies because the research data were complete or because the amount of missing data and the reasons for their absence were described. There was uncertainty about the reporting bias and other sources of bias because no previously published trial protocols for the included studies were found.

The funnel plot appeared symmetric as a whole, because an asymmetric plot suggests a publication bias, which is usually positive. In our analysis results, the dots were approximately symmetrically scattered around the pooled effect size (vertical line), indicating that there was no significant publication bias in our review (Fig. 3).

Overall Effect of tDCS

The pooled results on combining all 10 RCTs showed that tDCS was effective for swallowing function (SMD = 0.66, 95% CI = 0.40 to 0.92, $P < 0.00001$) in stroke patients. The I^2, a measure of statistical heterogeneity, was 22%, indicating good homogeneity between all trials. The pooled results showed that of the four trials found to have a small effect size,[10,16–18] three were positive[10,16,17] and one was negative (SMD = −0.13, 95% CI = −1.12 to 0.86).[18] One trial had a moderate positive effect size (SMD = 0.62, 95% CI = −0.01 to 1.26)[15] and five trials had large positive effect sizes ranging from 0.81 to 1.35.[9,11,12,14,26] Of these, only four trials were statistically significant (Fig. 4).

Acute Versus Chronic Stroke Patients

On further subgroup analysis on the stroke stages (acute vs. chronic stroke), we found a moderate positive effect size (SMD = 0.56, 95% CI = 0.28 to 0.85) in chronic stroke patients and a large positive effect size (SMD = 1.03, 95% CI = 0.54 to 1.52) in acute stroke patients. Both were statistically significant. The I^2 values for these two groups were 19% and 0%, respectively (Fig. 5).

Effect of Different tDCS Stimulation Schemes on Swallowing Function

On further subgroup analysis using tDCS on the affected, unaffected, or bilateral hemispheres, we found that compared with anodal tDCS in the affected hemisphere or anodal tDCS in the bilateral hemispheres, patients with anodal tDCS in the

TABLE 1. Characteristics of the included studies

Article, Year	Sample Size	Mean Age, yr	Sex	Stroke Type	Country/ Region	Intervention	Stimulation Site	Duration of Treatment	Dosage	Electrode Size, cm^2	Main Outcome Measure
Ahn et al.[17] (2017)	26	64	11 F/15 M	Chronic poststroke	Korea	Anodal to both hemispheres	Pharyngeal motor cortex	20 mins, 10 d	1 mA	25	DOSS
Kumar et al.[9] (2011)	14	70	7 F/7 M	Acute poststroke	America	Anodal to unaffected	Inferior sensorimotor cortex and premotor brain regions	30 mins, 5 d	2 mA	15	DOSS
Lai[14] (2017)	40	67.8	19 F/21 M	Chronic poststroke	China	Anodal to affected	Oral region of brain	20 mins, 20 d	0–2 mA	NA	Kubota Water Swallowing Test
Pingue et al.[16] (2018)	40	65.25	20 F/20 M	Chronic poststroke	Italy	Anodal to affected, cathodal to unaffected	Pharyngeal motor cortex	30 mins, 10 d	2 mA	25	DOSS and PAS
Shigematsu et al.[12] (2013)	20	65.8	7 F/13 M	Chronic poststroke	Japan	Anodal to affected	Pharyngeal motor cortex	20 mins, 10 d	1 mA	35	DOSS
Suntrup-Krueger et al.[11] (2018)	59	68.05	25 F/34 M	Acute poststroke	Germany	Anodal to unaffected	Pharyngeal motor cortex	20 mins, 4 d	1 mA	35	FEDSS, DSRS, and FOIS
Wang et al.[15] (2019)	40	62.8	12 F/28 M	Chronic poststroke	China	Anodal to unaffected	Pharyngeal motor cortex	40 mins, 10 d	1 .5 mA	35	MMASA
Wang et al.[13] (2020)	28	61.8	7 F/21 M	Chronic poststroke	China	Anodal to both hemispheres	Bilateral esophageal cortical area	40 mins, 20 d	1 mA	25	FDS, FOIS, and PESO
Yang et al.[18] (2012)	16	71	6 F/10 M	Chronic poststroke	South Korea	Anodal to affected	Pharyngeal motor cortex	20 mins, 10 d	1 mA	25	FDS
Ko et al.[10] (2016)	60	NA	NA	Chronic poststroke	Korea	Anodal to both hemispheres	Pharyngeal motor cortex	20 mins, 10 d	1 mA	NA	DOSS

DSRS, Dysphagia Severity Rating Scale; F, female; FDS, Functional Dysphagia Scale; FEDSS, Fiberoptic Endoscopic Dysphagia Severity Scale; FOIS, Functional Oral Intake Scale; M, male; NA, not available; PAS, Penetration-Aspiration Scale.

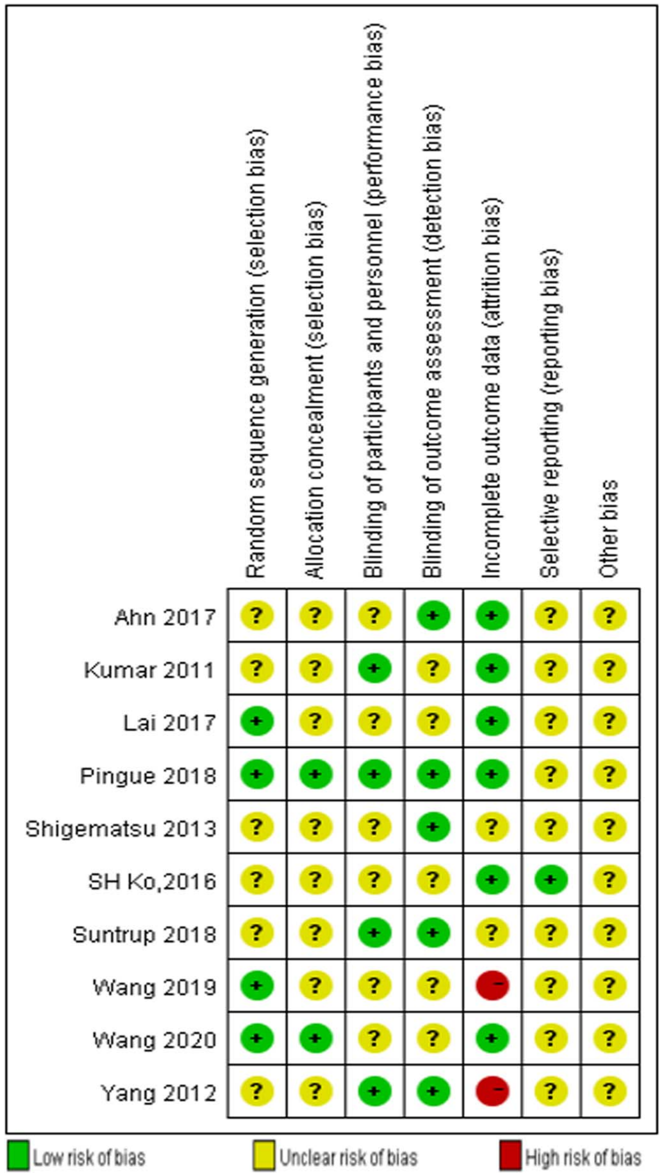

FIGURE 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

unaffected hemisphere were more likely to have greater improvement on the swallowing function test (SMD = 0.88, 95% CI = 0.49 to 1.27, $P < 0.0001$, $I^2 = 0\%$; Fig. 6). We pooled the results, combining the three RCTs in the group with anodal tDCS in the bilateral hemisphere (SMD = 0.68, 95% CI = 0.08 to 1.29, $P = 0.03$, $I^2 = 45\%$). Sensitivity analysis showed that the study by Wang et al.[13] (2020) was a major source of heterogeneity. After removing this study, the SMD for swallowing

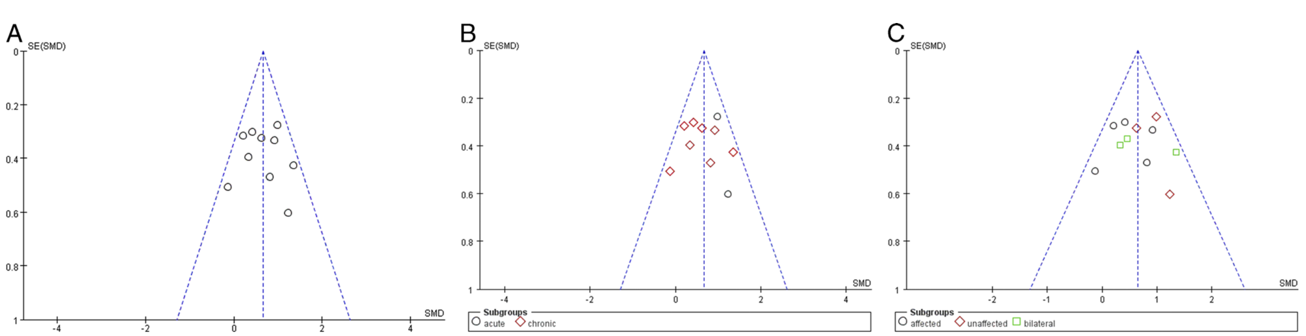

FIGURE 3. The funnel plot assesses publication bias in the 10 included trials. A, Overall analysis of 10 included trials. B, Subgroup analysis on the stroke stages (acute vs. chronic stroke). C, Subgroup analysis using tDCS on the affected, unaffected, or bilateral hemispheres.

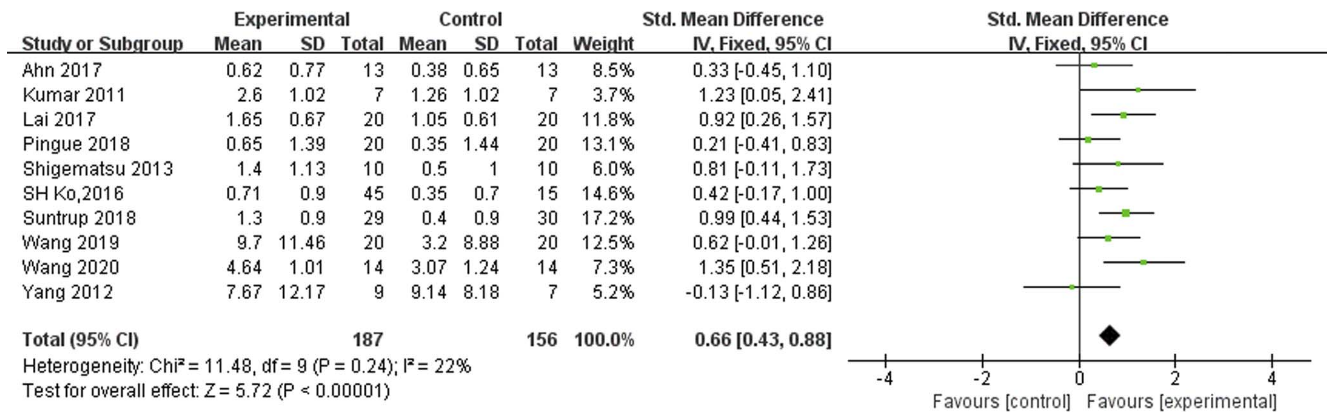

FIGURE 4. Forest plot of the overall effects of tDCS on poststroke dysphagia.

function improvement was 0.39 (95% CI = −0.14 to 0.92, $P = 0.151$, $I^2 = 0\%$).

DISCUSSION

Summary of Evidence

The present systematic review and meta-analysis of 10 studies showed that tDCS was associated with improved swallowing function in stroke patients. This was consistent with a previous review by Marchina et al.,[19] but some differences existed in the tDCS subgroup analysis. A moderate effect size of 0.66 (95% CI = 0.40 to 0.92, $P < 0.00001$) of tDCS on poststroke dysphagia was demonstrated in our systematic review. However, another meta-analysis reported a small effect size of 0.31 (95% CI = 0.03 to 0.59, $P = 0.03$).[19] Comparing the two meta-studies, we found that our study basically contains the previous literature, except for those from which we could not obtain full-text information. It is important to point out that most of the newly added literature were mainly published in China. One of these trials had a moderate positive effect size,[15] and two trials had large positive effect sizes ranging from 0.92 to 1.35.[13,14] Our research is very meaningful, because we have included new literature, and our results further confirm the effectiveness of tDCS on the recovery of dysphagia after stroke. However, the result of the specific effect size of tDCS on swallowing function after stroke still requires further confirmation with clinical trials of large sample sizes and with standardized methodology.

Acute Versus Chronic Stroke Patients

There was a statistically significant effect in both groups with relation to time after stroke: acute patients had a value of 1.03 (95% CI = 0.54 to 1.52, $Z = 4.09$, $P < 0.001$), and chronic patients had a value of 0.56 (95% CI = 0.28 to 0.85, $Z = 3.89$, $P = 0.0001$). Both were statistically significant. Based on the pooled results of our study, we can conclude that it is safe and effective in improving swallowing function in both acute and chronic stroke patients, and the effect of tDCS is larger

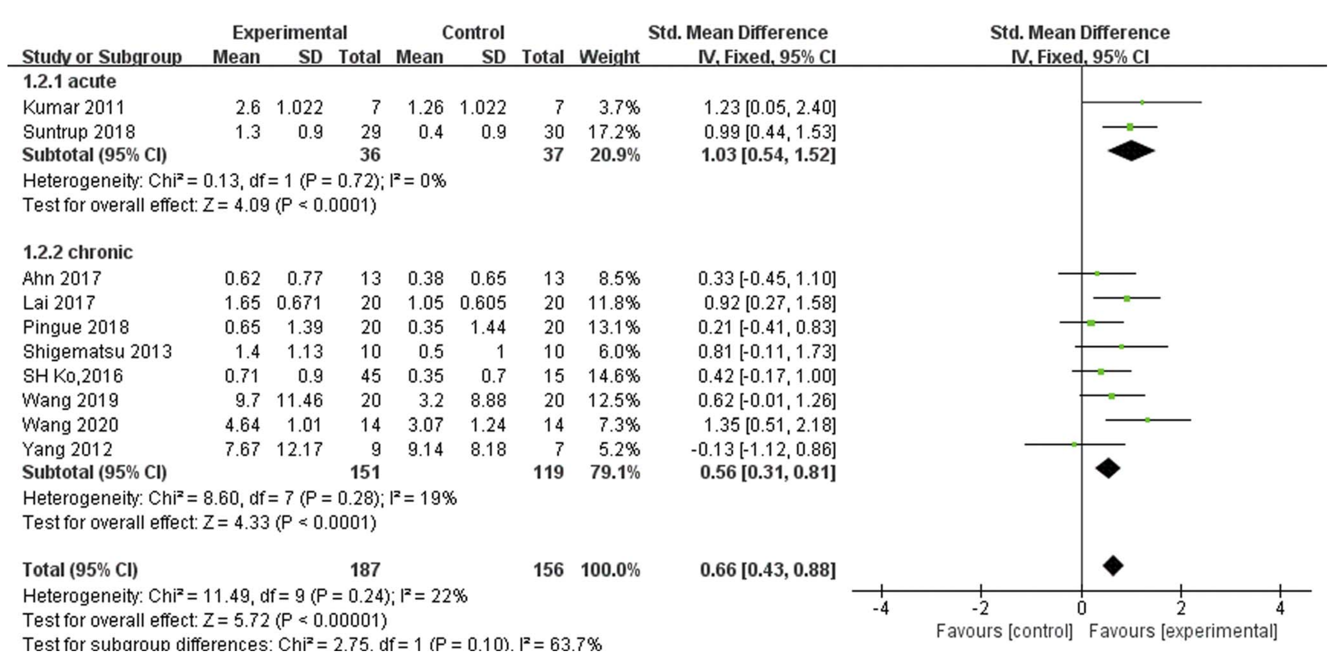

FIGURE 5. Forest plot of subgroup analysis, which shows the effect sizes for stimulation during the acute versus chronic stroke phase.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.3.1 affected								
Lai 2017	1.65	0.671	20	1.05	0.605	20	10.8%	0.92 [0.27, 1.58]
Pingue 2018	0.65	1.39	20	0.35	1.44	20	12.0%	0.21 [-0.41, 0.83]
Shigematsu 2013	1.4	1.13	10	0.5	1	10	5.5%	0.81 [-0.11, 1.73]
SH Ko,2016	0.71	0.9	45	0.35	0.7	15	13.3%	0.42 [-0.17, 1.00]
Yang 2012	7.67	12.17	9	9.14	8.18	7	4.7%	-0.13 [-1.12, 0.86]
Subtotal (95% CI)			**104**			**72**	**46.3%**	**0.47 [0.15, 0.79]**
Heterogeneity: Chi² = 4.47, df = 4 (P = 0.35); I² = 10%								
Test for overall effect: Z = 2.91 (P = 0.004)								
1.3.2 unaffected								
Kumar 2011	2.6	1.022	7	1.26	1.022	7	3.3%	1.23 [0.05, 2.40]
Suntrup 2018	1.3	0.9	29	0.4	0.9	30	15.7%	0.99 [0.44, 1.53]
Wang 2019	9.7	11.46	20	3.2	8.88	20	11.4%	0.62 [-0.01, 1.26]
Subtotal (95% CI)			**56**			**57**	**30.5%**	**0.88 [0.49, 1.27]**
Heterogeneity: Chi² = 1.12, df = 2 (P = 0.57); I² = 0%								
Test for overall effect: Z = 4.41 (P < 0.0001)								
1.3.3 bilateral								
Ahn 2017	0.62	0.77	13	0.38	0.65	13	7.7%	0.33 [-0.45, 1.10]
SH Ko,2016	0.7	0.82	15	0.35	0.7	15	8.8%	0.45 [-0.28, 1.17]
Wang 2020	4.64	1.01	14	3.07	1.24	14	6.7%	1.35 [0.51, 2.18]
Subtotal (95% CI)			**42**			**42**	**23.2%**	**0.67 [0.22, 1.11]**
Heterogeneity: Chi² = 3.66, df = 2 (P = 0.16); I² = 45%								
Test for overall effect: Z = 2.92 (P = 0.003)								
Total (95% CI)			**202**			**171**	**100.0%**	**0.64 [0.42, 0.85]**
Heterogeneity: Chi² = 11.79, df = 10 (P = 0.30); I² = 15%								
Test for overall effect: Z = 5.82 (P < 0.00001)								
Test for subgroup differences: Chi² = 2.54, df = 2 (P = 0.28), I² = 21.2%								

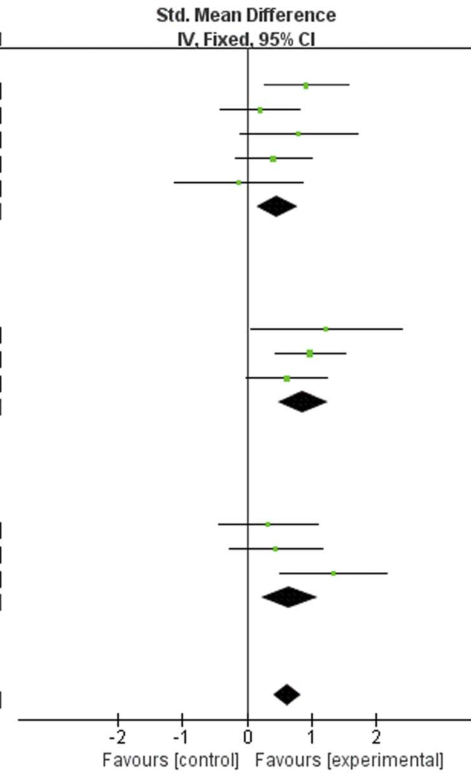

FIGURE 6. Forest plot of subgroup analysis, which shows the effect sizes for affected, unaffected, and bilateral hemisphere stimulation.

in the acute phase of stroke. The current research tends to consider neuromodulatory techniques (such as tDCS) as beneficial for cortical reorganization and increasing the pharyngeal activity of the contralateral motor cortex, which may be the potential mechanism of swallowing function rehabilitation during the acute phase of stroke.[19] Consistent with previous suggestions,[27–29] our meta-analysis findings support the hypothesis that the rehabilitation effects of tDCS on the contralesional hemisphere are different based on recovery stages. Interestingly, the previous meta-studies revealed a small nonsignificant effect size for both groups. Through further comparison, we found that the main outcome measures of the article that we did not include were Penetration-Aspiration Scale and Functional Oral Intake Scale, which was different from the two other studies. The I^2, a measure of statistical heterogeneity, was 50%, indicating medium heterogeneity between all trials. These factors may have affected the interpretation of the results. Furthermore, it is worth mentioning that both meta-analyses combined the chronic and subacute groups together because of their small sample size. Whether the effect of tDCS is greater in the acute versus chronic phase of stroke requires further investigation.

Effect of Different tDCS Stimulation Schemes on Swallowing Function

The subgroup analyses demonstrated that tDCS anodal to the affected hemisphere, unaffected hemisphere, and bilateral hemispheres can produce a significant effect size of swallowing function in stroke patients. Consistent with previous studies on the recovery of swallowing function after stroke, the reorganization of the swallowing motor cortex in the unaffected cerebral hemisphere can promote the improvement of swallowing function.[19] However, because swallowing has a bihemispheric representation, the reorganization of the damaged cerebral hemisphere may also play an important role in the recovery of swallowing function after stroke.[30–32] The weighted effect size for the unaffected hemisphere was large at 0.88, compared with the medium effect size of 0.47 for the affected hemisphere and 0.68 for bilateral hemispheres. This suggests that tDCS anodal to the unaffected hemisphere is superior to the affected hemisphere and bilateral hemispheres in improving swallowing function after stroke. This is consistent with the previous studies showing that the application of tDCS in the unaffected hemisphere may have some inherent advantages over applying it to the affected hemisphere, as the distribution of current density is unaffected by an underlying stroke with nonhomogeneous tissue, abnormal topography, or impaired intracortical connections.[33] Of course, this result requires further confirmation.

This meta-analysis still has the following limitations: (1) we excluded some studies published in languages other than English or Chinese, which led to the inclusion of research that is not very comprehensive; (2) the scale of outcome index used in this meta-analysis is different, and the tDCS stimulation scheme is also different, which leads to greater clinical heterogeneity; and (3) because of the relatively small number of studies that we eventually included and the inconsistent outcome indicators, these results cannot be confidently interpreted.

In conclusion, this systematic review and meta-analysis provided evidence that tDCS is likely to be effective for the recovery of dysphagia in poststroke patients in both the acute and chronic phases and that the effect of tDCS is larger when anodal to the unaffected hemisphere. More high-quality and large-scale studies in this area are required to determine whether this intervention has more significant benefits in certain patient subgroups and with specific stimulation protocols.

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