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Non-Invasive Brain Stimulation Progression in Post-Stroke Depression Treatment: A Systematic Review

ABSTRACT

Objective: Post-stroke depression (PSD) is the most common psychological disorder in patients with stroke. It not only seriously affects the patient's functional recovery, quality of life, and ability to return to society but also increases stroke recurrence rate and mortality. However, the effectiveness of drug treatment is unpredictable and associated with certain side effects and low compliance. Pharmacological therapy is limited. The field of noninvasive brain stimulation (NIBS) has recently made great progress in developing specific stimulation protocols to alleviate the symptoms of patients with PSD and might offer valid, alternative strategies.

Methods: We systematically searched PubMed, Embase, and the Cochrane Library for investigating the use of NIBS in the treatment of PSD. The methodological quality of selected studies was assessed according to the Risk of Bias 2 (ROB2).

Results: We identified 814 references in 3 databases. After excluding irrelevant and duplicate studies, 14 studies were included. According to the PRISMA checklist, 4 studies were overall comprehensive, 6 had some problems, and 4 had considerable problems with the presented information. The evidence was evaluated using ROB2, with 5 "low-risk" studies, 5 "some concerns" studies, and 4 "high-risk" studies included.

Conclusion: This review provides a comprehensive overview of the clinical trials reported in PSD. Noninvasive brain stimulation is a potentially promising treatment strategy. However, an optimal stimulation protocol needs to be formulated, and much work is required before NIBS can be widely applied in the clinic.

Keywords: Post-stroke depression, review, rTMS: repetitive transcranial magnetic stimulation, tDCS: transcranial direct current stimulation

Introduction

Over 12 million cases of stroke, a disease characterized by high morbidity and disability, were witnessed in 2019. Fortunately, the annual mortality rate is declining.[1] However, this trend means that a large number of patients with stroke sequelae will be encountered in clinical practice, and post-stroke depression (PSD) is one of the most common sequelae of stroke.[2] Compared with patients with stroke who do not have depression, those with PSD demonstrate a poorer long-term quality of life.[3] Currently, studies focusing on stroke sequelae have been conducted widely in the clinic.[4,5]

Approximately one-third of the patients with stroke will develop PSD, with a cumulative 5-year incidence of 39%-52%.[6] The primary clinical manifestations of PSD are affective disorder syndromes characterized by depressed mood, lack of interest, anhedonia, sleep disorder, etc., which are often accompanied by somatic symptoms.[7] Post-stroke depression can occur in any period after a stroke, with the highest prevalence in the first year and gradually decreasing thereafter. Nonetheless, >50% of the patients with PSD are diagnosed with mild depression accompanied by persistent depression (persistent depressed mood).[8]

Yanbin Zhang[1†]
Hongli Fang[2†]
Rui Wang[3]
Zhenggang Hu[1]
Mengqiu Qiu[1]

[1]Department of Neurology, the First People's Hospital of Linping District, Hangzhou, China
[2]Department of Neurology, The Affiliated Hospital of Hangzhou Normal University, Hangzhou, China
[3]Department of Emergency, the First People's Hospital of Linping District, Hangzhou, China

[†]Contributed equally to this work.

Corresponding author:
Mengqiu Qiu
choumengqiu@163.com

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To date, the pathogenesis of PSD has not been elucidated and involves several factors and disciplines, which mainly include neuropsychology, biology, anatomy, and sociology. Previous studies have considered PSD to be a pure cardiogenic reaction. The sudden occurrence of stroke affects the speech, limbs, and cognitive functions of the patients, affecting their ability to live independently, leading to a series of negative emotions, such as a sense of futility and despair. When the long-term psychological stress response exceeds their ability to cope with stress, psychological disorders tend to occur.[9,10] The "location hypothesis," one of the various hypotheses of the PSD mechanism, is widely accepted. The left frontal lobe and basal ganglia have been identified to be the key regions of PSD.[11] Further research confirmed that the "frontal subcortical circuit"[12] and "limbic cortical striatal pallidum thalamic circuit"[13] are the key networks that regulate emotional behaviors. Some studies have also stated that "neurotransmitter hypoxia" is one of the main reasons for PSD. As emotional behaviors are regulated by different neurotransmitters, especially monoamines (such as noradrenalin (NE), serotonin (5-HT), and dopamine (DA)), dysfunction under various conditions may lead to different types of mental symptoms such as depression.[14] Injury to specific brain regions (brainstem, thalamus, limbic system, and frontal cortex) after stroke leads to decreased secretion and bioactivity of 5-HT, NE, and DA, resulting in the occurrence of PSD.[15] The dynamic imbalance of glutamate and γ-aminobutyric acid *in vivo* can lead to dendrite remodeling and loss of glial cells, thus playing a role in the pathogenesis of PSD.[16] Studies have shown that psychosocial factors and neuroendocrine mechanisms are involved in the occurrence of PSD.[17-18] Furthermore, the response caused by inflammatory factors can stimulate the hypothalamus–pituitary–adrenal axis to release glucocorticoids. Increased levels of glucocorticoids can damage nerve cells, promote the degradation of tryptophan (5-HT precursor) and tyrosine (NE precursor), reduce the production of 5-HT and NE, and eventually result in PSD.[19]

A previous study has opined that depression in patients with neurological diseases is often more difficult to treat than that in general individuals.[20] Drug therapy, primarily using antidepressants, is undoubtedly the basis for clinical treatment. Selective serotonin reuptake inhibitors, noradrenaline and specific serotonergic antidepressants, selective serotonin and noradrenaline reuptake inhibitors, and tricyclic antidepressants[21-23] have been extensively applied as first-line drugs in the clinical treatment of PSD. However, the effectiveness of these drugs is unpredictable, and all of them are associated with certain side effects and low compliance.[24] Moreover, long-term antidepressant treatment can become a hidden danger for stroke recurrence. In addition, PSD interventions in the recently published Cochrane review indicated the absence of strong evidence that these drug interventions could effectively reduce depressive symptoms after stroke.[25] Therefore, a non-drug treatment strategy is an alternative worth exploring.

MAIN POINTS

- *Post-stroke depression (PSD) is the most common psychological disorder in patients with stroke.*
- *In recent years, noninvasive brain stimulation (NIBS), a non-pharmaceutical treatment approach, has attracted extensive attention among the scientific community as it is non-invasive and patient compliance is strong.*
- *This review was focused on relevant studies of patients with PSD treated using NIBS, especially the repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) techniques.*

In recent years, noninvasive brain stimulation (NIBS), a scheme in the field of non-drug therapy, has attracted extensive attention among the scientific community as it is non-invasive. NIBS can regulate neuroplasticity, explore the underlying pathogenesis, and can be customized according to the needs of individual patients.[26-28] Hence, this review was focused on the relevant studies of patients with PSD treated using NIBS, especially the repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) techniques.

Methods

Our research was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist guidelines. Only English language studies and published data were taken into consideration. This study was approved by Ethics Committee of Hangzhou Normal University (Approval No: 2021429625; Date: 29/12/2020).

Literature Search

Literature searches were performed across PubMed, Embase, and the Cochrane Library. Our literature search expressions were as follows: ((Transcranial Magnetic Stimulation or TMS) or (Repetitive Transcranial Magnetic Stimulation or rTMS)) or ((transcranial direct current stimulation or tDCS) or (noninvasive brain stimulation or NIBS)) AND (post-stroke depression or PSD) AND (Depression or Depressive Symptoms or Mood Disorder) AND ((Stroke or Post-stroke or Ischemic Stroke or Hemorrhagic Stroke or Acute Cerebrovascular Accidents)).

Subsequently, the abstracts were screened and articles selected for full-text evaluation were reviewed.

Study Selection

We identified relevant articles for the review based on the population, intervention, comparison, outcome, and study framework. Additionally, we conducted a thorough review of reference lists from selected articles to ensure comprehensive coverage of relevant studies beyond those identified through electronic search methods.

To be included in the review, studies had to meet the following criteria: (1) the study was a primary research investigation, with rTMS and tDCS utilized as treatments for patients diagnosed with PSD; (2) the evaluation of PSD treatment efficacy must have been conducted using at least one outcome measure specifically for PSD and the reported study must have provided sufficient statistical information; (3) the study needed to be published in a peer-reviewed journal and available in English; (4) participants involved in the study should have been aged ≥18 years; and (5) studies were presented as clinical trials.

Data Extraction

We used the PICOS tool according to the PRISMA guidelines. We paid particular attention to patients' intervention, machine type, comparator, outcomes, study design, and stimulation parameters. The information extracted included: author, study type, country, literature size, sample size, treatment group, technical index, and outcome indicators.

Risk of Bias in Included Studies

Our included studies were assessed by using the Cochrane Risk of Bias Tool for Trials (ROB2), which evaluates bias across 5 dimensions: (1) the randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of the outcome, and (5) selection of the reported result. Each included study underwent blinded assessment for risk of bias by 4 authors, with disagreements resolved through discussion with an independent author. Two blinded and independent authors independently assessed each included study, with any disagreements resolved by a third author.

Results

Results of the Search

A total of 814 records were identified, 291 records were excluded as duplicates and another 439 references were excluded as irrelevant. After a full-text review of the remaining 23 studies, we excluded 3 that had no controls, 1 that had patients with other diseases, and 2 that were not clinical trials. However, due to the limited number of selected studies, 3 case reports were also included for a comprehensive discussion. Finally, we included 14 studies.[29-42] (Figure 1).

Characteristics of Included Studies

According to the PRISMA checklist, 4 studies were overall comprehensive, 6 had some problems, and 4 had considerable problems with the information provided.

There were 6 randomized controlled trials (RCTs), 5 clinical trials, and 3 case reports, all of which were written in English. Five random-control studies and 2 prospective clinical trials that applied high-frequency rTMS targeted on the left dorsolateral prefrontal cortex (DLPFC) for treatment of PSD were finally selected.[31-37] Only 1 clinical trial used low-frequency stimulation to treat patients with PSD.[38] Patients with PSD were assessed using Hamilton Depression Scale (HAMD)-17 and Beck Depression inventory (BDI) as shown in Table 1A.

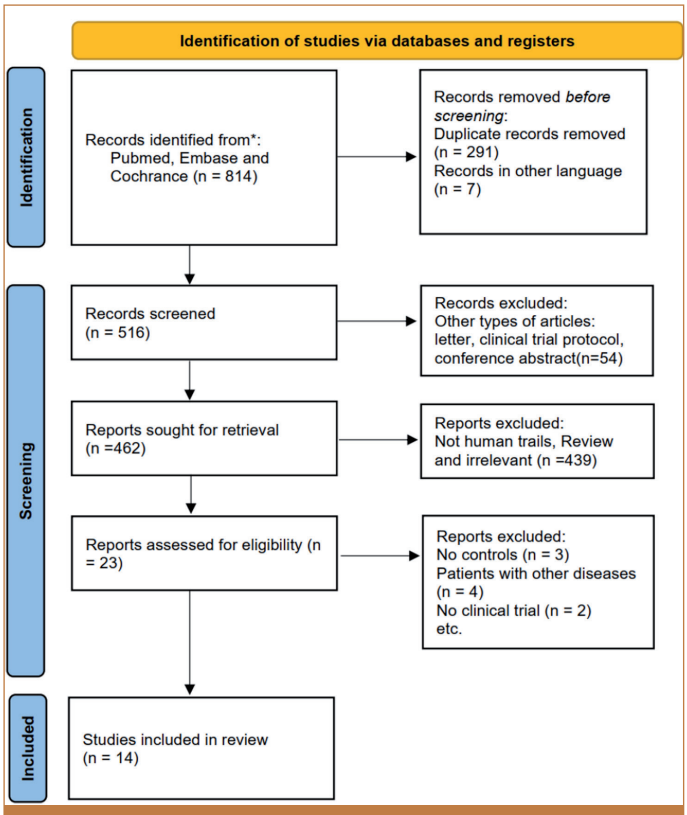

Figure 1. PRISMA flowchart of study selection and reasons for exclusion.

Six experimental studies on tDCS for PSD involved placing the anode electrode on the scalp corresponding to the left DLPFC, while attaching the cathode to the right DLPFC following the International 10-20 electroencephalogram (EEG) System. The tDCS was administered at an intensity of 2 mA for 30 minutes in 4 studies within the active/experimental group, whereas in Li's and Hassan's studies, patients received anodal tDCS stimulation at an intensity of 2 mA for only 20 minutes[41,42] (Table 1B).

Reporting of the Quality Evaluation Results

The PRISMA statement project report was adopted, with the title item covered in full in 14 articles (Item 1), and structured summaries selected for reporting in 10 articles (Item 2). The theoretical foundations were fully presented in all 14 articles (Item 3). Seven articles supplemented the reporting on the objectives, and 6 reported partially (Item 4). In the method and registration section, 7 articles reported completely, and 2 reported partially (Item 5). All 14 articles reported on the source of information (Item 7) and the research screening process (Item 9). The inclusion criteria (Item 6) and data elements (Item 11) were partially reported. Due to the type of study, study bias (Item 12) and other analyses (Item 16) were not reported in 14 articles. Most articles reported summary impacts indicators (Item 13) and statistical methods (Item 14). All 14 articles fully reported the research characteristics in the results section (Item 18). Most reported on the selection of the study (Item 17) and the integration of the results (Item 21). Four individual cases (Item 20). In the discussion section, all 14 articles reported summaries of evidence (Item 24) and 11 reported limitations (Item 25). Twelve articles reported the source of funding (Table 2).

Main Outcome Measures

Most studies focused on the efficacy and safety of NIBS in PSD patients, mainly improving depressive symptoms, neurological function, cognitive function, daily living activities, accompanying symptoms, and adverse effects.

Improvement of Depressive Symptoms: Of the 14 included articles, 7 used HAMD scores as the outcome indicator. Intervention measures included: (1) tDCS alone, (2) tDCS + sham, (3) rTMS alone, (4) rTMS + sham, and (5) rTMS combined with antidepressant drugs + antidepressant drugs. All studies reported that the HAMD score of the treatment group was higher than that of the control group after treatment.

Recovery of Cognitive Function: Four articles explored the impact of NIBS on cognitive function in PSD patients, all of which used the MMSE scale for assessment. Intervention measures were divided into 4 types: (1) rTMS alone, (2) rTMS combined with antidepressant drugs, (3) tDCS alone, and (4) tDCS + sham. Four studies showed that the treatment significantly improved cognitive function in PSD patients compared with controls.

Improvement of the Ability to Perform Activities of Daily Living: The 6 articles included in this review examined the effects of NIBS on the daily living activities on patients with post-stroke depression, assessed using the BDI scale. All 5 studies showed that the treatment

Table 1A. rTMS characteristics of included systematic reviews.

Study Design	Number of Subjects	Therapy	Target	Frequency	Total Pulse	Duration of Treatment	Interval Between Each rTMS Train	Outcome Measurement
RCT	32	rTMS	DLPFC_L	High (5 Hz)	40 000	4 weeks	25 seconds	HAMD-17
RCT	100	rTMS	DLPFC_L	High (5 Hz)	32 000	8 weeks	56 seconds	HAMD-17
RCT	11	rTMS	DLPFC_L	High (10 Hz)	30 000	2 weeks	26 seconds	BDI, PHQ-9
RCT	24	rTMS	DLPFC_L	High (10 Hz)	10 000	2 weeks	60 seconds	HAMD-17
Prospective clinical trial	6	rTMS	DLPFC_L	High (20 Hz)	31 200	2 weeks	12 seconds	HAMD
Prospective clinical trial	15	rTMS	DLPFC	High (10 Hz), Low (1 Hz)	High-40 000, Low-12 000	4 weeks	25 seconds	HAMD-17
Prospective RCT	22	rTMS	DLPFC_L	High (10 Hz), Low (1 Hz)	4500	2 weeks	10 seconds	BDI
Clinical trial	62	rTMS	Primary motor cortex	Low (1 Hz)	26 400	2 weeks	Unknown	BDI

BDI, Beck Depression inventory; DLPFC_L, dorsolateral prefrontal cortex_left; HAMD, Hamilton Depression Scale; PHQ-9, Patient Health Questionnaire-9; RCT, randomized controlled trial; rTMS, repetitive transcranial magnetic stimulation.

group had better improvement in daily living activities than the control group. However, 1 study reported that there was no significant difference in recovery of daily activities between the treatment group and the control group after treatment.

PSD with Aphasia Symptoms Improvement: Only 1 article included in this review examined the influence of NIBS on aphasia symptoms in patients with PSD, and the study showed that NIBS could reduce Aphasic Depression Rating Scale (ADRS) scores and significantly improve depressive symptoms.

Adverse Reactions: Twelve articles in this review reported side effects following NIBS, and patients tolerated NIBS well. Minor side effects such as loss of appetite, local discomfort, anxiety, fatigue, and dry mouth were not significantly different.

Study Quality

For all the studies, risks for the bias of included studies were low or some concern to moderate. Although 4 articles showed high risk, the included articles did not randomly assign patients or were case reports, which may be the reason for suggesting high risk. In addition, there was no loss of outcome data. The details are shown in Figure 2.

Discussion

Transcranial Magnetic Stimulation for PSD

TMS Technique: Transcranial Magnetic Stimulation (TMS) uses electromagnetic induction as an efficient and almost painless approach to generate current in the brain that can discharge the target neuronal population.[43] In 1985, Barker et al[44] reported the use of the single-pulse TMS technique in which the "type 8" insulated coil is placed on the surface of the skull. The strong current that circulates in the coil can produce a pulsed magnetic field of a certain strength. This magnetic field acts on the cerebral cortex via the scalp and skull and regulates the action potential of neurons via the sensory current, thereby affecting the electrophysiological activity of neurons.

In contrast to TMS, rTMS is a potential therapeutic method that can alter and regulate cortical activity after the stimulation period.[33] Different stimulation frequencies or pulse sequences can be applied in this technique, which acts on motor and nonmotor brain regions in various stimulation forms, exerting effects on brain activity.[43] In most cases, low-frequency (≤1 Hz) stimulation inhibits the activity of the target brain region, whereas high-frequency (>1 Hz) stimulation activates the target brain region.[45,46]

Table 1B. tDCS characteristics of included systematic reviews.

Study	Year	Country	Study Design	Number of Subjects	Therapy	Anode	Cathode	Current Density (A/m^2)	Number of Sessions	Outcome Measurement
Bueno et al[39]	2011	USA	Open label case report	1	tDCS	DLPFC_L	DLPFC_R	2 mA, 30 min	10	MADRS BDI, MMSE, MOCA
Valiengo et al[29]	2017	Brazil	RCT	48	tDCS	DLPFC_L	DLPFC_R	2 mA, 30 min	12	HDRS-17, MADRS, the Young Mania Rating Scale
An et al[42]	2017	Korea	Controlled	40	tDCS	DLPFC_L	DLPFC_R	2 mA, 30 min	20	BDI
Li et al[40]	2019	China	Clinical trail	26	tDCS	DLPFC_L	DLPFC_R	2 mA, 20 min	20	An emotional face sex judgment task and a "1-back" working memory task
Hassan et al[41]	2021	Nigeria	Case report	1	tDCS	DLPFC_L	DLPFC_R	2 mA, 20 min	10	BDI,VAS, DN4Q
Valiengo et al[30]	2016	Brazil	Open label and uncontrolled	4	tDCS	DLPFC_L	DLPFC_R	2 mA, 30 min	12	ADRS,

tDCS, transcranial direct current stimulation; DLPFC_L, dorsolateral prefrontal cortex_left.

Table 2. PRISMA declaration entries report conditions.

	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Item 24	Item 25	Item 26	Item 27
Y	14	10	14	7	7	0	14	7	14	10	0	0	11	13	0	0	10	14	0	4	13	5	11	14	11	14	12
PY	0	0	0	6	2	14	0	0	0	1	14	0	1	1	0	0	2	0	1	6	0	1	1	0	0	0	0
N	0	4	0	1	5	0	0	7	0	3	0	14	3	0	14	14	2	0	13	4	1	8	2	0	3	2	2

Item 1 title; item 2 structured abstract; item 3 theoretical basis; item 4 introductory purpose; item 5 protocol and registration; item 6 inclusion criteria; item 7 sources of information; item 8 search; item 9 study selection; item 10 data extraction; item 11 data item; item 12 individual study bias; item 13 effect indicators; item 14 synthetic outcome methods; item 15 inter-study bias methods item 16 supplemental analysis methods; item 17 study screening; item 18 study characteristics; item 19 risk of intra-study bias; item 20 individual study results; item 21 synthetic results; item 22 inter-study bias results; item 23 supplemental analysis results; item 24 evidence summary; item 25 limitations; item 26 conclusions; item 27 funding; Y: yes; PY: probably yes; N: no.

High-Frequency rTMS for PSD: A recent study[47] observed that the DLPFC is an important node in the dorsal attention network that can affect emotional responses by changing the higher-order perceptual attention system and that damage to it can induce depression. Another study has also established the effectiveness of high-frequency rTMS in the treatment of PSD.[48] Hence, it is evident that most researchers use high-frequency rTMS to treat the DLPFC region. The frequency used in this method is from 5 Hz to 20 Hz. The results of a recent randomized controlled study[31] revealed that Hamilton depression scale (HAMD) scores in both rTMS and sham stimulation groups were significantly reduced after the treatment, but the rTMS group demonstrated a more obvious improvement. Another study[32] documented that high-frequency (5 Hz) rTMS treatment in combination with citalopram was beneficial in improving depression and neuropsychological function, which has promising potential in the treatment of PSD.[32] This method can significantly improve patients' mini-mental state examination scores, suggesting that rTMS can considerably strengthen the antidepressant effect of drug treatment. Hordacre et al[33] stimulated the DLPFC region of patients using high-frequency rTMS (10 Hz). The results showed that the lower the baseline depression level of the patients, the more obvious was the increase in the θ frequency connectivity between the left DLPFC and the right parietal region and the improvement in the Beck Depression Inventory (BDI) score. Compared with the sham stimulation group, the depressive symptoms of patients in the rTMS group were reduced after the treatment.[33] In a randomized controlled study, Gu et al[34] treated patients using 10 Hz rTMS, which significantly reduced the severity of anxiety, depression, and stroke and substantially improved the cognitive ability and daily living ability of the patients.[34] Furthermore, in a small-sample prospective study involving high-frequency accelerated rTMS,[41] patients were stimulated using 20 accelerated rTMS for 4 days, 5 times a day, for a total of 20 times. The findings signified that the HAMD score of the patients was significantly reduced and that the symptom relief rate reached 100%, which persisted during the 3-month follow-up. These results suggest that accelerated rTMS is a safe and feasible treatment for PSD.[35] However, owing to the small population size of the study, this conclusion remains speculative.

The benefits of high-frequency rTMS were validated in a meta-analysis[49] that involved 10 randomized controlled trials and 524 patients with significant effects, but most of the effects were short-term. Furthermore, this study[49] failed to identify the source of high heterogeneity and the sample size was small, which may limit the universality and validity of the findings. Only 2 studies[33,34] have explored the long-term effects of rTMS intervention. Therefore, studies with larger samples and those that consider other influencing factors are required to evaluate the effectiveness and safety of NIBS in patients with depression after stroke.

Low-Frequency rTMS for PSD: Few studies have so far focused on the treatment of PSD using low-frequency rTMS. A recent study[43] used 10 Hz and 1 Hz rTMS to stimulate the DLPFC of patients, and the results showed significant changes in HAMD scores in both groups. Nevertheless, the alterations in the high-frequency and low-frequency groups were different. The effect of high-frequency stimulation is more significant in the short term, whereas that of low-frequency stimulation is more lasting.[36] Moreover, studies have compared the therapeutic effects of high-frequency and low-frequency rTMS. Kim et al[44] applied

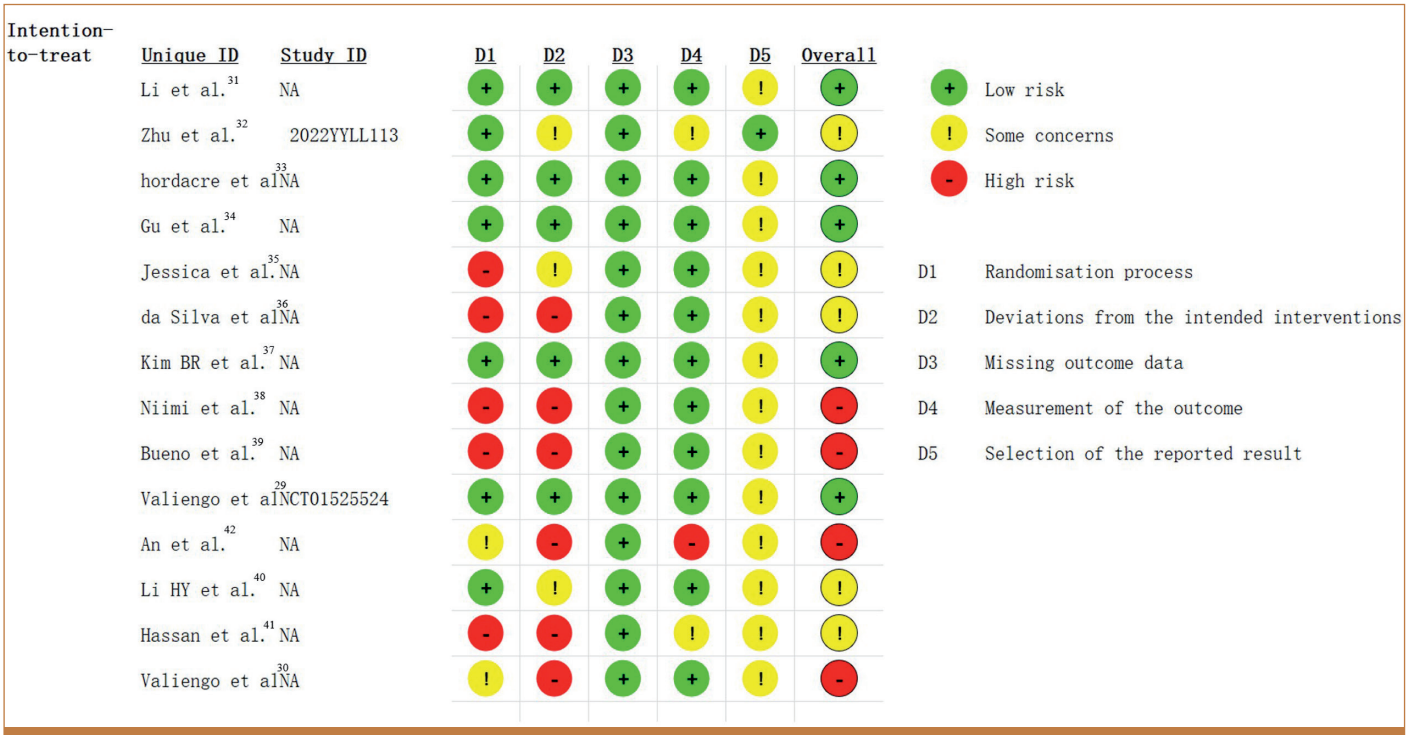

Figure 2. Risk of bias (2.0).

different frequencies to stimulate the DLPFC of patients, and the results indicated that the BDI scores of the low-frequency group were significantly higher than those of the high-frequency group. An rTMS study[38] on neural pathways in stroke suggested that low-frequency (1 Hz) stimulation of the contralateral primary motor cortex can change body tryptophan content and increase the kynurenine level, which may be more effective in improving depression. These findings provide novel insights for subsequent investigations on low-frequency rTMS. However, the treatment of PSD with low-frequency stimulation needs to be further explored.

tDCS

The tDCS Technique: Transcranial direct current stimulation is a type of NIBS that provides a long (10-20 minutes) but weak (1-2 mA) current to the brain tissue via electrodes placed on the scalp to regulate neuronal excitability in a polarity-specific manner.[50] This method primarily serves a regulatory function by modulating the likelihood of neuronal firing through adjustment of membrane polarity. Specifically, anodal tDCS typically depolarizes the resting membrane potential of neurons, leading to increased spontaneous neuronal firing rate and heightened cortical excitability. In contrast, cathodal tDCS diminishes cortical excitability by inducing hyperpolarization of the resting membrane potential, thereby reducing neuronal firing rate.[51] These polarity-dependent cortical excitability changes observed in the motor cortex are hypothesized to depend on the neuroplasticity mechanisms (NMDA-dependent processes), similar to potential long-term potentiation (LTP) and long-term depression.[52] Certain investigations have established that brain-derived neurotrophic factor plays a key role in LTP formation and is regulated by tDCS.[53] In addition, the regulatory function of tDCS also demonstrates persistence.[54] A previous study has shown that tDCS anodal stimulation for 5 minutes can increase motor cortex excitability, which lasts for more than a few minutes.[55] Furthermore, the levels of some neurotrophic factors and immune-inflammatory factors have been reported to be associated with the effects of tDCS.[56]

Based on the wide application of tDCS in neuropsychiatric diseases (such as depression and Parkinson's disease)[57] and its characteristics of low cost, simple operation, minimal side effects, and good tolerability, this technique has received extensive attention.[58]

tDCS for PSD: Bueno et al[39] first reported the effect of tDCS on the emotion and cognition of patients with PSD. In a subsequent randomized controlled study, Valiengo et al[29] observed that the HAMD score was reduced in patients with PSD treated with tDCS; furthermore, depressive symptoms were relieved, and no adverse reactions occurred. In a study examining the mechanism of tDCS,[55] the anode and cathode were placed in the left and right prefrontal cortex of patients. The findings revealed that the concentration of oxyhemoglobin was significantly increased after the treatment compared with that before the treatment. The depressive symptoms of the patients were relieved, which suggests that tDCS may alleviate depression in patients with PSD by improving aerobic metabolism in the prefrontal cortex.[40]

As PSD is often accompanied by central pain, Hassan et al[41] identified that patients' depression scores decreased after tDCS treatment. Pain symptom-related scores also decreased to some extent, and a long-term improvement in mood was induced. Aphasia is one of the common complications after a stroke, and tDCS may improve the precision of picture naming in patients with aphasia after a stroke. A study[30] reported that the scores of the stroke aphasic depression questionnaire and the aphasic depression rating scale decreased under tDCS intervention and that the depressive symptoms of all patients were significantly improved.[30]

Furthermore, Hao et al[59] and An et al[42] observed that tDCS provides promising results in the treatment of PSD. However, a single sample report is not universal and should be confirmed by performing larger studies. The results of the systematic review and analysis by Li et al[60] also showed that tDCS can improve PSD, but the heterogeneity of the stimulation schemes was relatively high, and which stimulation scheme is the best remains unclear.

In the past decade, both rTMS and tDCS have emerged as potentially promising treatment strategies. However, a significant limitation of the studies conducted thus far is the considerable variability in their methodology, including differences in the number of sessions, site of stimulation, current intensity or coil type, and outcome measures. Additionally, publication bias remains a salient issue, with a tendency to preferentially publish positive or statistically significant results while potentially underreporting neutral findings.

Moreover, there remains a lack of comprehensive understanding regarding the precise mechanism of action of repeated non-invasive cerebellar stimulation. Subsequent research should prioritize uncovering the underlying cellular processes, including potential alterations in gene expression, protein synthesis, channel pump regulation, and modulation of receptors and/or neurotransmitters. Additionally, it is imperative to conduct further investigations to determine the optimal timing for follow-up stimulation, evaluate the feasibility of remotely supervised stimulation at home within a larger patient population, and assess whether synchronous exercise training interventions or medication can enhance the effects of non-invasive stimulation.

In summary, the NIBS techniques of rTMS and tDCS are potentially promising treatment strategies, although much work needs to be done before they can be widely applied in the clinic.

Post-stroke depression is a disease that involves multiple factors that are physiological, psychological, and social. It is an important factor that seriously hinders the rehabilitation of a patient's neurological function and daily living ability. The improvement of patients' mood aids in rehabilitation after stroke, improves their quality of life, reduces the recurrence rate of stroke, and indirectly saves medical resources and reduces economic costs. Although the NIBS technique offers several advantages, its intervention tends to be empirical. In terms of treatment strategy, except for DLPFC stimulation site selection, other factors such as stimulation intensity, stimulation time, and treatment course are different, and there are few long-term follow-up studies. In addition, most studies are small-sample, single-center trials with potential selection bias. Furthermore, the assessment methods of NIBS in the treatment of PSD rely on subjective semiquantitative psychological scales. Hence, objective methods, such as functional imaging, should be added to evaluate the treatment effect via functional connectivity in the brain or the integrity of nerve fiber bundles.[61] In the future, advancements in the noninvasive brain–computer interface technique are expected to transform the diagnosis and treatment of depression.[62]

Ethics Committee Approval: *This study was approved by Ethics Committee of Hangzhou Normal University (Approval No: 2021429625; Date: 29/12/2020).*

Availability of Data and Materials: *The data are extracted from published studies and are available in the article, and the datasets are not subject to restrictions.*

Informed Consent: *N/A.*

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PRISMA 2020 Check list

Section and Topic	Item#	Checklist Item	Location Where Item is Reported
TITLE			
Title	1	Identify the report as a systematic review.	page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	page 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	page 1-2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	page 1-2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	page 2-3
Information sources	6	Specify all databases, registers, websites, organizations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	page 2-3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	page 2-3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and, if applicable, details of automation tools used in the process.	page 2-3
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and, if applicable, details of automation tools used in the process.	page 2-3
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	page 2-3
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	page 2-3
Study risk of bias assessment	11	Specify the methods used to assess the risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and, if applicable, details of automation tools used in the process.	page 2-3
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.	none
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	page 2-3
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	none
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Line 118-119
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	none
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).	none
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	none
Reporting bias assessment	14	Describe any methods used to assess the risk of bias due to missing results in a synthesis (arising from reporting biases).	page 2-3
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	page 2-3

Section and Topic	Item#	Checklist Item	Location Where Item is Reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	page 3-4
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	page 3-4
Study characteristics	17	Cite each included study and present its characteristics.	page 3-4
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	page 3-4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	page 3-4
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	page 3-4
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	page 3-4
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	page 3-4
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	page 3-4
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	page 3-4
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	page 3-4
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	page 4-7
	23b	Discuss any limitations of the evidence included in the review.	page 4-7
	23c	Discuss any limitations of the review processes used.	page 4-7
	23d	Discuss implications of the results for practice, policy, and future research.	page 4-7
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	None
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	None
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	None
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	page 7
Competing interests	26	Declare any competing interests of review authors.	page 7
Availability of data, code, and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	page 7

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71