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Review

Can non-motor outcomes be improved in chronic stroke? A systematic review on the potential role of non-invasive brain stimulation

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ABSTRACT

Background: Non-invasive brain stimulation induces changes in spontaneous neural activity in the cerebral cortex through facilitatory or inhibitory mechanisms, relying on neuromodulation of neural excitability to impact brain plasticity. This systematic review assesses the state-of-the art and existing evidence regarding the effectiveness of NIBS in cognitive recovery among patients with chronic stroke.

Materials and methods: We conducted a systematic search, following PRISMA guidelines, for articles published from January 2010 through September 2023. We searched the following databases: PubMed, Embase, Cochrane Database of Systematic Reviews, PEDro, Rehab Data, and Web of Science.

Results: Our electronic searches identified 109 papers. We assessed and included 61 studies based on their pertinence and relevance to the topic. After reading the full text of the selected publications and applying predefined inclusion criteria, we excluded **32** articles, leaving **28** articles for our qualitative analysis. We categorized our results into two sections as follows: (1) Cognitive and emotional domains (11 studies), (2) language and speech functions (**16** studies).

Conclusion: Our findings highlight the potential of NIBS, such as tDCS and rTMS, in the cognitive, linguistic, and emotional recovery of post-stroke patients. Although it seems that NIBS may work as a complementary tool to enhance cognitive and communication abilities in patients with stroke –also in the chronic phase- evidence on behavioural outcomes is still poor. Future studies should focus on this important issue to confirm the effectiveness of neuromodulation in chronic neurological diseases.

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1. Introduction

Stroke is one of the leading causes of long-term disability worldwide, due to its sequalae on cognitive, language, and motor functions. In Europe, around 1.1 million inhabitants suffer a stroke each year, and ischemic aetiology is accounted for approximately 80 % of cases (Béjot et al., 2016). Cognitive impairments after stroke can be present in 96 % of cases (Sun et al., 2014), and this includes attention, memory, language, and orientation problems. According to Al-Qazzaz et al. (2014), the most affected cognitive domains are attention and executive functions. Moreover, some authors reported that cognitive deficits are often associated with a decrease in the long-term survival rate (Perna et al., 2015), and increased depression symptoms. This latter aspect can interfere not only in achieving independent living, but also in participation in rehabilitation paths. Recent studies have emphasized the effectiveness of Non-invasive brain stimulation (NIBS) in promoting rapid intervention on cognitive and motor components, particularly in patients suffering from chronic stroke. In fact, NIBS induces changes in spontaneous neural activity in the cerebral cortex through facilitatory or inhibitory mechanisms, relying on neuromodulation of neural excitability to impact brain plasticity. Various methods of NIBS are available. Transcranial electrical stimulation (tES) is a safe and non-invasive

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technique involving the delivery of very low-intensity electric current to the scalp usually via two or more electrodes (anode-depolarizing; or cathode-hyperpolarizing) (Lefebvre et al., 2015). In its modern form, tES uses a battery-powered stimulator to pass weak (1 to 4 mA) electrical currents between electrodes attached to the scalp (Krause et al., 2023). Depending on the type of current delivered, it is possible to distinguish between direct current (tDCS), alternating current (tACS), or random noise (tRNS) electrical stimulation (Moliadze et al., 2019). tES can modify the excitability state of neurons affected by current flow, and the induced changes can persist beyond stimulation for periods ranging from a few minutes to hours, depending on the parameters used, making it useful for rehabilitation (Inukai et al., 2016; Meinzer et al., 2016).

On the other hand, Transcranial Magnetic Stimulation (TMS) uses a magnetic field to stimulate or inhibit specific brain areas, and it has proven highly effective in treating various disorders, including Resistant Depression and Obsessive-Compulsive Disorder (Meinzer et al., 2016; Gu et al., 2019). The magnetic field is generated by a coil, a metal spiral, through which a current flow, producing an intense magnetic field (1–4 T). While short-lived, it is effective in modulating or inducing excitability/inhibition. TMS can be single, paired, or repetitive cycles (rTMS), with the latter sending high and low-frequency trains repetitively, potentially resulting in prolonged changes after stimulation. A recent type of magnetic stimulation is intermittent Theta Burst Stimulation (iTBS), which utilizes low-intensity stimulation for greater treatment accessibility. iTBS uses a coil to excite or inhibit neurons in the cerebral cortex with magnetic pulses, each stimulation lasting less than 5 min, with 4 to 8 stimulations performed per day. iTBS offers advantages such as lower costs and reduced time required for effective treatment (Sasaki et al., 2017).

Some authors have suggested that NIBS is useful in treating cognitive dysfunction and improving attention, memory, and executive function (Allendorfer et al., 2021; Smith et al., 2009; Kang et al., 2009; Chi et al., 2010). However, while there is a wealth of studies related to motor improvement following NIBS, data pertaining to the cognitive domains are still under evaluation.

This systematic review aims to evaluate the effectiveness of NIBS in cognitive, emotional, speech, and language rehabilitation in patients with chronic stroke. Additionally, we paid attention on investigating the anatomical areas targeted by brain stimulation in the included studies.

2. Methods

We conducted this systematic review to explore the existing evidence on NIBS in patients with chronic stroke to promote cognitive recovery. We summarized the results of all published studies following the guidelines established by Pollok et al. (2018). This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines 12 and has been registered with the Prospective Register of Systematic Reviews under the number CRD42023458370 (PROSPERO 2023).

2.1. PICO model

We utilized the PICO (Population/Problem, Intervention, Comparison, Outcome) model to formulate our research question. Our inquiries were twofold: "Is NIBS a viable and safe tool in the neurorehabilitation of chronic stroke patients?" and "What are the optimal treatment approaches for these patients?"

The population encompassed adults (>18 years) afflicted by chronic stroke (both ischemic and haemorrhagic). Our intervention entailed various non-invasive neuromodulation techniques (e.g., TMS and tDCS). As for comparison, we included sham or placebo stimulation in the control group, enabling comparative analysis of active intervention effects. Outcomes encompassed any cognitive and non-motor demonstrated by patients alongside treatment efficacy.

This framework guided our study approach, providing a structured pathway to evaluate the efficacy and safety of NIBS in chronic stroke rehabilitation. It facilitated rigorous research structuring, focusing on essential elements to address research inquiries and derive meaningful conclusions.

2.2. Search strategy and information sources

A systematic search, according to PRISMA guidelines (Page et al., 2020), was conducted for all peer-reviewed articles published from January 2010 through September 2023, using the following databases: PubMed, Embase, Cochrane Database of Systematic Reviews, Pedro, Medline, PsycINFO, RehabData, and Web of Science. The following terms were used: ("chronic stroke"[MeSH Terms] OR ("ictus"[All Fields]) AND ("neuromodulation"[All Fields] OR " NIBS "[All Fields] OR "transcranial non-invasive stimulation" [All Fields] OR "tDCS"[All Fields] OR "Transcranial magnetic stimulation"[All Fields] OR "TMS" [All Fields] OR " Transcranial electrical stimulation"[All Fields] OR "tE"[All Fields] OR " intermittent Theta Burst Stimulation" [All Fields] OR "iTBS"[All Fields]) AND ("neuroplasticity"[MeSH Terms]).

All articles were reviewed based on titles, abstracts and full texts, by two investigators (MGM and MB), who independently performed data collection to reduce the risk of bias (i.e., the bias of missing results, publication bias; time lag bias; language bias). These researchers read the full-text articles deemed suitable for the study and in case of disagreement on the inclusion and exclusion criteria, the final decision was made by a third researcher (RCS). The list of articles was then refined for relevance, revised, and summarized, with the key topics identified from the summary based on the inclusion/exclusion criteria.

2.3. Eligibility criteria

The inclusion criteria were: (i) adult patients with chronic stroke (≥6 months); (ii) an applied approach to cognitive and non-motor functions; (iii) the English language; and (v) published in a peer-reviewed journal.

We have excluded articles describing theoretical models, methodological approaches, algorithms, and basic technical descriptions. Additionally, we excluded: (i) animal studies; (ii) conference proceedings or reviews; and (iii) studies involving children; (iv) case reports and reviews.

2.4. Selection and data collection processes

To minimize the risk of bias, the review process was conducted under strict blinding conditions. Two independent reviewers (MGM and MB) were blinded to the authors' identities and affiliations during the screening and data extraction process. This blinding procedure aimed to mitigate potential sources of bias, such as publication bias, and language bias. All search results were imported into an online database (RYYAN) (Ouzzani et al., 2016), where the reviewers independently assessed each study's relevance based solely on its content and methodology.

Furthermore, the agreement of the included studies based on the inclusion/exclusion criteria between the two blinded reviewers (MGM and MB) was rigorously evaluated using the kappa statistic. The kappa score, with a threshold for substantial agreement set at > 0.61, was employed to assess the level of concordance between the reviewers. This statistical criterion ensured a robust evaluation of inter-rater reliability, highlighting a substantial level of agreement in the data extraction process despite the blinding protocol.

2.5. Data items and data extraction

In accordance with PRISMA guidelines, rigorous procedures were employed for data extraction to ensure comprehensive coverage of relevant information. Data items encompassed in the extraction process included first author, year of publication, study design, sample size, use of control groups, details of interventions and controls, baseline characteristics, type of outcomes measured, adverse events, major findings. To maintain consistency and accuracy, two independent reviewers performed the data extraction process. Any discrepancies between reviewers were resolved through discussion or consultation with a third reviewer if necessary. This meticulous approach ensured a thorough and reliable synthesis of the available evidence, enhancing the robustness of our review.

3. Results

3.1. Assess quality of included studies – risk of bias

The risk of bias in controlled studies was assessed using a revised Cochrane risk of bias (RoB 2) tool 13, which comprises five domains: i) bias arising from the randomization process, ii) bias due to deviations from the intended intervention, iii) bias due to missing outcome data, iv) bias in the measurement of the outcome, v) bias in the selection of the reported result. We identified numerous studies with a low risk of bias and robust methodologies.

3.1.1. Cognitive and emotional domains

The most prevalent risk of bias was found in Domain 1, which relates to randomization processes. In this domain, only 7 out of the 12 studies were judged to have a low risk of bias (Sterne at al., 2019; Tsai et al., 2020; Lu et al., 2015; Farahmandi Najafabadi et al., 2022; Richard et al., 2022; Kolskår et al., 2021; Ko et al., 2022). These studies did not adequately disclose their randomization procedures. Studies with a low risk of bias provided information related to the type of procedure used and the accuracy of recruitment.

In Domain 2, all but one study reported blinding or specified who was responsible for blinding (Li et al., 2021).

For Domain 3, some concerns about controlling bias were identified in five studies (Gu et al., 2017; Tsai et al., 2020; Li et al., 2021; Kim et al., 2015; Shaker et al., 2018), where the authors did not use scales such as the CONSORT to address potential bias.

In both Domains 4 and 5, we observed a low risk of bias, except for some concerns raised in two studies in Domain 4 (Lu et al., 2015; Li et al., 2021) and one study in Domain 5 (Lu et al., 2015). These concerns were related to the limited and inconsistent outcome measures not aligning with the study's objectives.

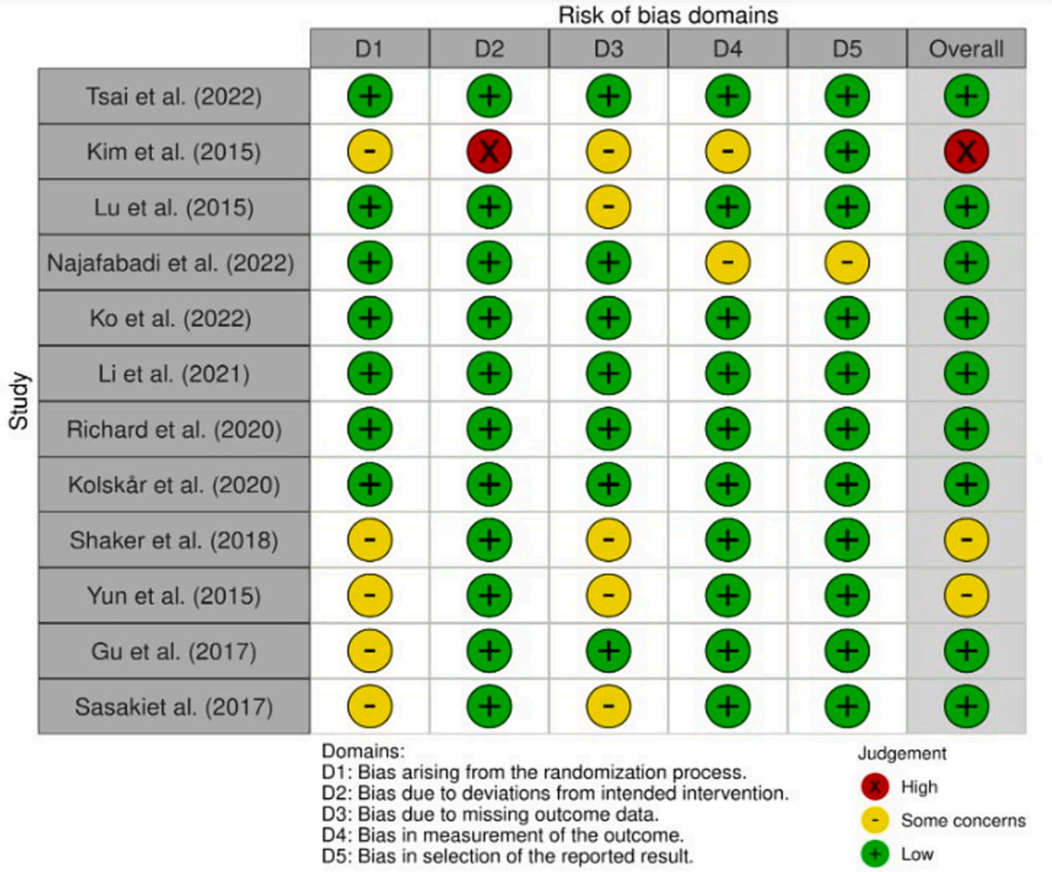
In summary, the majority of the included studies provided a robust categorical quality analysis, and the dataset was considered sufficient for the planned sensitivity analyses (Fig. 1).

3.1.2. Speech and language functions

We identified a risk of bias across all domains of RoB2. In particular, two studies (Hara et al., 2017; Abo et al., 2012) exhibited a risk of bias in both randomization (domain 1) and blinding (domain 2) (Hara et al., 2017; Abo et al., 2012; Goh et al., 2015). The most prevalent risk of bias was observed in domain 3, with nine studies failing to provide a CONSORT diagram/checklist (Yun et al., 2015; Barwood et al., 2013; Hara et al., 2017; Abo et al., 2012; Goh et al., 2015; Pestalozzi et al., 2018; Richardson et al., 2015; Baker et al., 2010; Xie et al., 2022). Lastly, two studies reported a risk of bias in both domain 4 and domain 5 (Fig. 2) (Abo et al., 2012; Xie et al., 2022).

3.2. Synthesis of evidence

Electronic searches identified 109 papers. We assessed and included **60** studies based on their pertinence and relevance to the topic. After reading the full text of the selected publications and applying the predefined inclusion criteria, we excluded **32** articles, leaving **28** articles



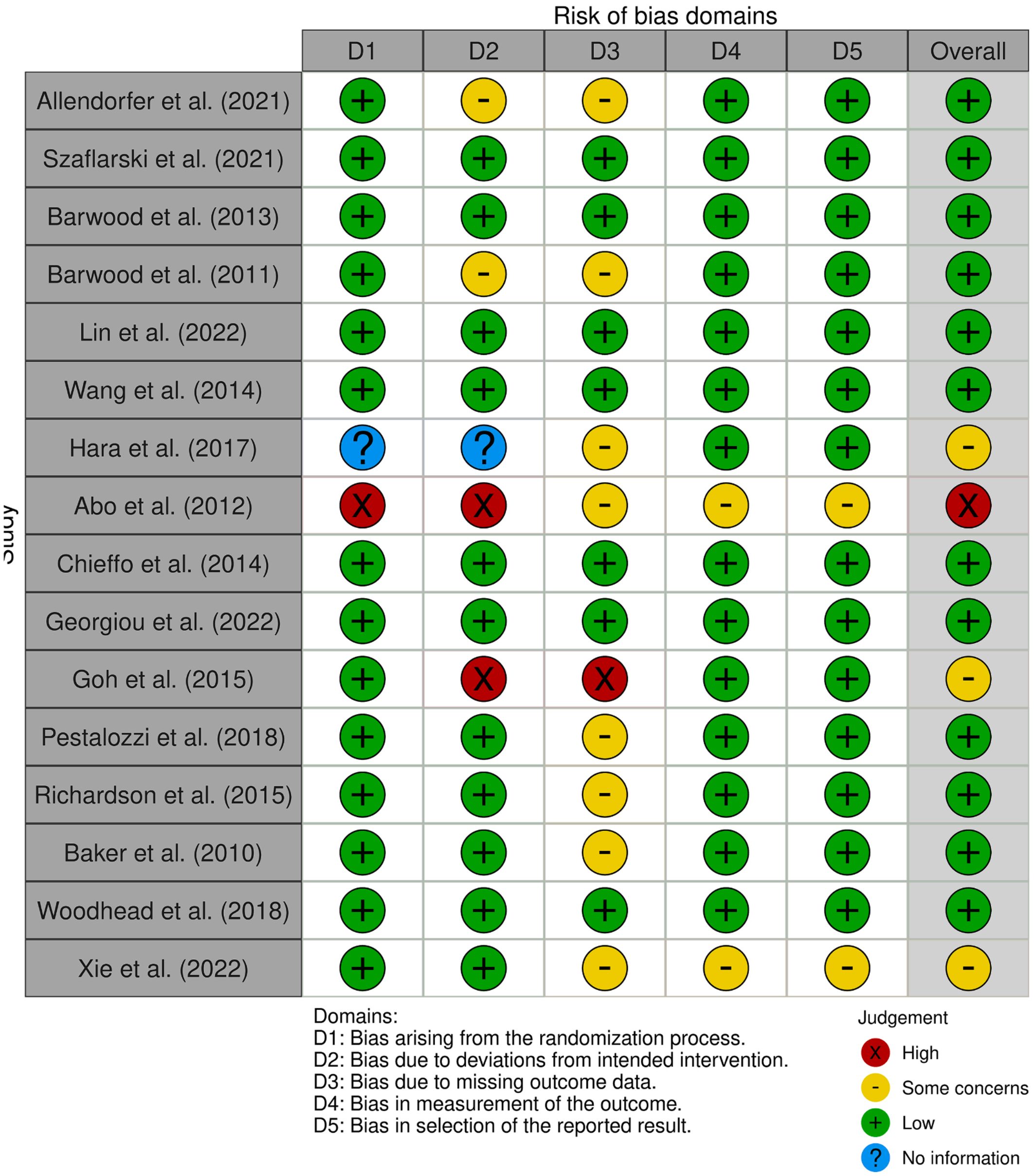
Risk of bias domains

Study	D1	D2	D3	D4	D5	Overall
Tsai et al. (2022)	+	+	+	+	+	+
Kim et al. (2015)	-	X	-	-	+	X
Lu et al. (2015)	+	+	-	+	+	+
Najafabadi et al. (2022)	+	+	+	-	-	+
Ko et al. (2022)	+	+	+	+	+	+
Li et al. (2021)	+	+	+	+	+	+
Richard et al. (2020)	+	+	+	+	+	+
Kolskår et al. (2020)	+	+	+	+	+	+
Shaker et al. (2018)	-	+	-	+	+	-
Yun et al. (2015)	-	+	-	+	+	-
Gu et al. (2017)	-	+	+	+	+	+
Sasakiet al. (2017)	-	+	-	+	+	+

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
X High
- Some concerns
+ Low

Fig. 1. Shows theRisk of Bias (RoB) of studies regarding cognitive domains.



Risk of bias domains

Study	D1	D2	D3	D4	D5	Overall
Allendorfer et al. (2021)	+	-	-	+	+	+
Szaflarski et al. (2021)	+	+	+	+	+	+
Barwood et al. (2013)	+	+	+	+	+	+
Barwood et al. (2011)	+	-	-	+	+	+
Lin et al. (2022)	+	+	+	+	+	+
Wang et al. (2014)	+	+	+	+	+	+
Hara et al. (2017)	?	?	-	+	+	-
Abo et al. (2012)	X	X	-	-	-	X
Chieffo et al. (2014)	+	+	+	+	+	+
Georgiou et al. (2022)	+	+	+	+	+	+
Goh et al. (2015)	+	X	X	+	+	-
Pestalozzi et al. (2018)	+	+	-	+	+	+
Richardson et al. (2015)	+	+	-	+	+	+
Baker et al. (2010)	+	+	-	+	+	+
Woodhead et al. (2018)	+	+	+	+	+	+
Xie et al. (2022)	+	+	-	-	-	-

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
X High
- Some concerns
+ Low
? No information

Fig. 2. Shows theRisk of Bias (RoB) of studies regarding language and speech domains.

for our qualitative analysis. We categorized our results into **2** sections as follows: (1) Cognitive and behavioral domains (12 studies), (2) language and speech functions (**16** studies). For more details, please refer to Fig. 3.

3.2.1. *Cognitive and emotional domains*

We identified 12 articles focusing on the use of NIBS to enhance cognitive and emotional abilities (Table 1).

Specifically, our search revealed 10 studies on the application of NIBS in cognitive functions (Tsai et al., 2020; Lu et al., 2015; Farahmandi Najafabadi et al., 2022; Richard et al., 2022; Kolskår et al., 2021; Ko et al., 2022; Li et al., 2021; Kim et al., 2015; Shaker et al., 2018; Yun et al., 2015), and 2 Randomised Controlled Trials (RCTs) on emotional and behavioral abilities (1 on depression Gu et al., 2017; and 1 on apathy Sasaki et al., 2017). The studies included three types of NIBS (rTMS, tDCS, and iTBS – combined with rTMS), and 3 studies combined NIBS with computerized cognitive training (Lu et al., 2015; Farahmandi Najafabadi et al., 2022; Richard et al., 2022).

In the realm of cognitive domains, we found 7 studies using on rTMS (Tsai et al., 2020; Kim et al., 2015; Lu et al., 2015; Farahmandi Najafabadi et al, 2022; Gu et al., 2017; Sasaki et al. 2017; Li et al., 2012). We also identified 5 studies featuring tDCS stimulation, including those that combined tDCS with computerized cognitive training (Ko et al., 2022; Richard et al., 2022; Shaker et al., 2018; Yun et al., 2015; Kolskår et al., 2020).

For instance, Kim et al. (2015) conducted an RCT study on 34 S patients admitted to the hospital with hemispatial neglect. They found that ten sessions of low frequency rTMS on the left parietal cortex could have beneficial effects on hemispatial neglect when compared to a single rTMS session (Li et al., 2021). Another RCT study was carried out by Lu et al. (2015) with 44 patients, administering rTMS frequency (1 Hz stimulation) to stimulate the right side of the dorsal prefrontal cortex (dlPFC). The authors demonstrated that rTMS could improve cognitive and memory functions in stroke patients. Similarly, Tsai et al. (2020) implemented an RCT stimulating the dlPFC with both rTMS and iTBS (5 Hz) and observed the effectiveness of these stimulations in addressing cognitive impairment, attention, and memory function (Sterne et al., 2019). In addition, Li et al. (2021) conducted a prospective study

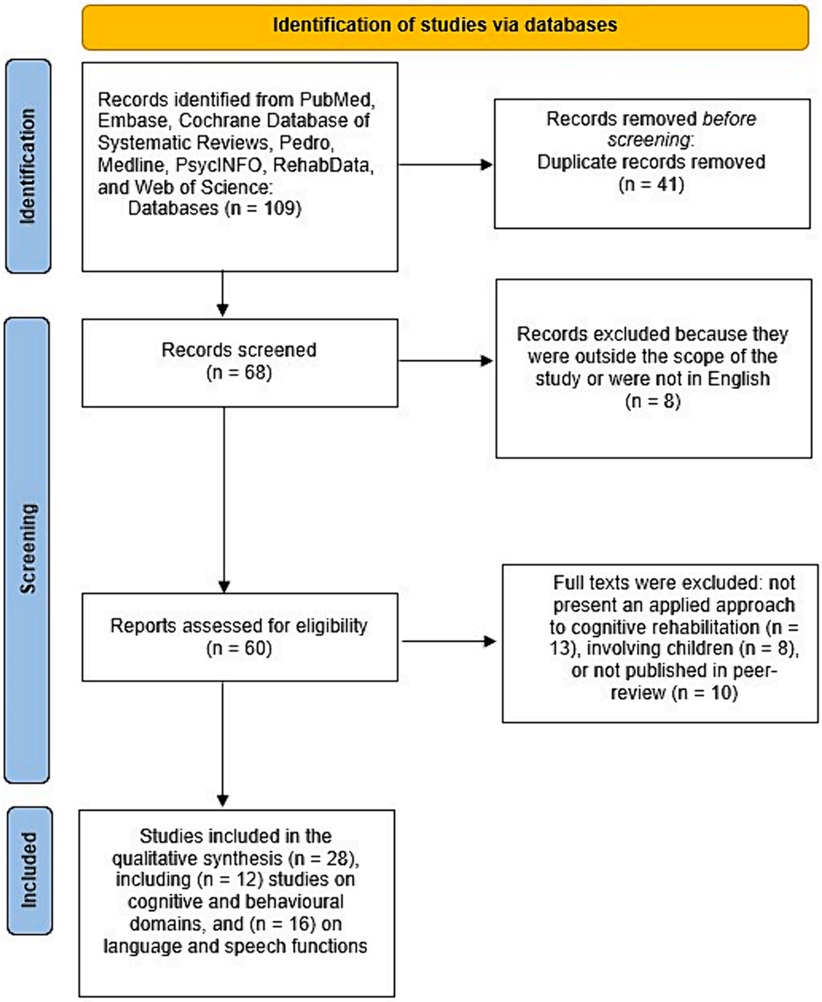


Fig. 3. PRISMA Flow Chart.

stimulating the same area and observed the effectiveness of rTMS on 65 patients, evaluating that NIBS can be effective for stimulating cognitive domains and hormonal levels (Ko et al., 2022).

Farahmandi Najafabadi et al. (2022) performed an RCT, combining computerized cognitive training (CCRT), using Captain's Log software (adult module), with rTMS stimulation of the left dlPFC. The authors showed that CCRT can be effective in rehabilitating working memory, and this effect is maximized when it is used in combination with rTMS implemented in the left dlPFC area (Lu et al., 2015). The effectiveness of the combination of NIBS and CCRT has been observed by other authors (Farahmandi Najafabadi et al., 2022; Richard et al., 2022; Kolskår et al., 2021; Kim et al., 2015; Shaker et al., 2018). Ko et al. (2022) applied tDCS stimulation associated with the CogTx program to 26 patients with chronic stroke. They highlighted that tDCS and CCRT are potentially effective for increasing cognitive outcomes (Kolskår et al., 2021). Similar results were obtained by Shaker et al. (2018), who conducted an RCT with 40 patients combining tDCS and CCRT with the Rehacom system, observing the potential effect of these two tools in cognitive rehabilitation (Kim et al., 2015). In line with these findings, Richards et al. (2020) conducted an RCT combining Cogmed with tDCS and evaluated MRIs, indicating that longitudinal brain age prediction based on automated brain morphometry is feasible and reliable in stroke patients (Farahmandi Najafabadi et al., 2022). Finally, Kolskår et al. (2021) conducted a prospective study with 48 patients, observing that combined tDCS and CCRT could improve cognitive outcomes in chronic stroke patients (Richard et al., 2020). Unlike previous authors, Yun et al. (2015) conducted an RCT evaluating the effect of tDCS alone on the left temporal lobe in 45 patients and observed positive effects on the patients' auditory memory (Shaker et al., 2018).

On the other hand, we identified only two studies regarding the effectiveness of NIBS in improving emotional and behavioural abilities. In particular, Gu et al. (2017) conducted an RCT with sessions of high frequency (10 Hz) rTMS to the Left dlPFC. Additionally, Sasaki et al. (2018) conducted a Pilot RCT to evaluate the effect of high frequency rTMS performed in the dorsal anterior cingulate cortex to the medial prefrontal cortex, highlighting its usefulness in addressing apathy due to stroke.

In addition, we found that only Lu et al. (2015), reported some adverse events (as showed in Table 1), like transient headache, and dizziness, in two patients treated with rTMS. Otherwise, six out of twelve studies did not report any adverse event to the neuromodulation treatment, while four studies stated that there were no side effects to the treatment.

3.2.2. *Speech and language functions*

We found 16 articles focused on using NIBS to enhance speech and language functions in post-stroke patients. Specifically, our search revealed – randomized studies and one pilot study. The studies included three types of NIBS (rTMS, iTBS, and tDCS or tACS) (see Table 2).

TMS was applied in 16 studies (3 RCTs and one pilot study) to improve speech abilities in post-stroke aphasia (Allendorfer et al., 2021; Szaflarski et al., 2021; Barwood et al., 2011; Barwood et al., 2013; Lin

Table 1
Shows the principal studies concerning NIBS applied to cognitive and behavioural domains.

Studies	Study design	Sample size	Intervention	Type and Areas of NIBS, domains	Type of stroke Disease duration	Outcomes	Adverse events	Major findings	PEDro score
Tsai et al. (2020)	RCT	44 rTMS = 14 iTBS = 15 Sham = 15	In each group stimulation was applied in 10 sessions over 10 consecutive weekdays	rTMS iTBS Left DLPFC, attention, and memory function	Ischemic/ haemorrhagic stroke From 18 to 38 months	RBANS BDI Cognitive domains and hormonal levels	no seizure or other adverse effects	rTMS and iTBS at 5 Hz are effective for post-stroke cognitive impairment	9
Kkiim et al. (2015)	RCT	34 EG: 19 CG: 15	EG had a total of ten rTMS, five times a week for 2 weeks. CG had low frequency rTMS only once time	rTMS, unaffected parietal cortex, hemispatial neglect	haemorrhagic stroke average duration 17.42 months	MagPro® line bisection test, letter cancelation test and Ota's task	Not reported	10 sessions of low frequency rTMS on the left parietal cortex could have beneficial effects on the hemispatial neglect	7
Lu et al. (2015)	RCT	44 EG: 22 CG: 22	EG: rTMS treatment once a day, 5 days a week for 4 weeks. CG all parameters were the same as for real treatment, inducing no magnetic stimulation	rTMS Right DLPFC, cognitive and memory functions	Ischemic/ haemorrhagic stroke average duration 61.33 months	MoCA LOTCA RBMT	Transient headache and Dizziness in 2 rTMS patient Headache in 1patient sham	Low frequency rTMS on the right side of the DLPFC could improve cognitive and memory functions in stroke patients	9
Farahmandi Najafabadi et al. (2022)	RCT	18 EG: 9 CG: 9	Both groups participated in 15 six-minute rTMS sessions, 3 days a week. In CG the waves didn't reach the brain. Both groups received CCRT	rTMS Captain's Log software Left DLPFC, working memory	Ischemic/ haemorrhagic stroke Average duration 12.72	WAIS test N-back subscale	Not reported	CCRT can be effective in rehabilitating the working memory. The effect is maximized when it is used in combination with rTMS	7
Ko et al. (2022)	RCT	26 EG:12 CG: 14	EG: tDCS (constant current of 2 mA) was administered for 30 min with CogTx. CG: The training was identical to EG, but they receive sham tDCS	TDCS CogTx, DLPFC General Cognition	Ischemic/ haemorrhagic stroke ≥6 months after onset	SCWT TMT Go/No Go test COWAT K-BNT K-DRS-2	no serious adverse effects	The association of tDCS and CCRT is potentially effective for increasing the cognitive outcomes	10
Richard at al. (2020)	RCT	54 EG: 20 CG. 24	All patients completed a CCRT (25 online) EG: tDCS during the first 20 min of CCRT sessions. CG: Sham stimulation.	tDCS Cogmed Systems	ischemic or hemorrhagic stroke and transient ischemic attacks (TIA) ≥6 months after onset	MoCA SCWT WASI CVLT-II D-KEFS	Not reported	Longitudinal brain age prediction based on automated brain morphometry is feasible and reliable in stroke patients.	11
Shaker et al. (2018)	RCT	40 EG: 20	EG: tDCS in combination with CCRT. CG: sham	tDCS RehaCom,	ischemic cerebrovascular stroke in the domain of carotid system duration of	RehaCom FIM	Not reported	Stimulation of the DlPFC can be very useful in improving the patient's	7

(*continued on next page*)

Table 1 (*continued*)

Studies	Study design	Sample size	Intervention	Type and Areas of NIBS, domains	Type of stroke Disease duration	Outcomes	Adverse events	Major findings	PEDro score
		CG: 20	tDCS in combination with the same CCRT	DlPFC, Attention concentration memory Logical reasoning	illness at least 6 months from stroke onset			cognition, especially in association with CCRT.	
Yun et al. (2015)	RCT	45 EG2: 15 CG: 15	EG1: Left-FTAS, anode stimulation CG: sham group	tDCS Right-FTAS memory	Ischemic/ haemorrhagic stroke ≥6 months after onset	CNT	Not reported	The results confirmed that the application of tDCS to the left temporal lobe effectively improved the patients' auditory memory	6
Gu et al. (2017)	RCT	24 EG: 12 CG: 12	EG: 10 sessions of high-frequency (10 Hz) stimulation; CG: 10 sessions of sham stimulation	rTMS Left DLPFC depression	cerebral infarcts, intracerebral hemorrhages; 10.2 ± 2.5 months from onset	BDI, HAM-D MI-UE MI-LE MBC FAC	No adverse side effects	rTMS is a beneficial therapeutic modality	9
Sasaki et al. (2017)	Pilot RCT	13 EG: 7 CG: 6	EG: 5 sessions of either high frequency rTMS for 5 days CG: sham stimulation for 5 days	rTMS dACC MPFC Apathy	supratentorial intracerebral hemorrhages ≥6 months after onset	AS QIDS	no adverse effects	The application of high frequency rTMS over the dACC and mPFC could be a useful intervention for apathy due to stroke.	8
Li et al. (2012)	Prospe-ctive	65 EG: 33 CG: 32	EG and CG performed conventional rehabilitation and cognitive training. In addition, EG received to rTMS and CG have sham stimulation	rTMS DLPFC contralateral, cognitive domains and hormonal levels	Ischemic/ haemorrhagic stroke ≥6 months after onset	MMSE MoCA MBI Serum Thyroid Hormones Levels	Not reported	rTMS treatment (contralateral DLPFC, 1 Hz) increases T3, FT3 and TSH levels and improves scores of cognitive domains	10
Kolskår et al. (2020)	Retrospective	48 EG: 26 CG: 22	EG: CCT and tDCS (1 mA). CG: CCRT and sham tDCS, with 40 s active stimulation (1 mA)	tDCS Cogmed left DlPFC, working memory	stroke with ischemic or hemorrhagic etiology ≥6 months after onset	NIHSS TOAST MMSE WASI	No adverse effects	Combined treatments improve cognitive outcomes.	10

Apathy Scale (AS), Acute Stroke Treatment (TOAST), Beck Depression Inventory (BDI), Computerized Neuropsychological Test (CNT), computerized cognitive rehabilitation (CCRT), Controlled Oral Word Association Test (COWAT), California Verbal Learning Test (CVLT-II), Delis-Kaplan Executive Function System (D-KEFS), Dorsal Anterior Cingulate Cortex (dACC), Functional Ambulatory Category (FAC), Functional independence measure (FIM), fronto-temporal anode stimulation (FTAS), Hamilton Depression Rating Scale (HAM-D), Loewenstein Occupational Therapy of Cognitive Assessment (LOTCA), Medial Prefrontal Cortex (mPFC), Modified Barthel Index (MBI), modified Brunnstrom Classification (MBC), Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), National Institutes of Health Stroke Scale (NIHSS), Quick Inventory of Depressive Symptomatology (QIDS) Rivermead Behavior Memory Test (RBMT), Korean Mini-Mental State Examination (K-MMSE), Stroop Word Test (SCWT), Trail Making Test (TMT), upper (MI-UE) and lower limb Motricity Indices (MI-LE), Korean-Boston Naming Test (K-BNT), Korean version of the Dementia Rating Scale-2 (K-DRS-2), Wechsler Adult Intelligence Scale (WAIS), Wechsler Abbreviated Scale of Intelligence (WASI).

et al., 2022; Wang et al., 2014; Hara et al., 2017; Abo et al., 2012; Chieffo et al., 2014; Georgiou et al., 2022; Goh et al., 2015; Pestalozzi et al., 2018; Richardson et al., 2015; Baker et al., 2010; Woodhead et al., 2018; Xie et al., 2022). Two studies used iTBS (Allendorf et al., 2021; Szaflarski et al., 2021), demonstrating that iTBS resulted in language improvements. Allendorfer et al. (2021) observed that iTBS led to changes in fMRI and improvements in post-stroke aphasia. These results were confirmed by Szaflarski et al. (2021), who showed that the tool applied to the left frontal lobe can enhance aphasia and boost cortical plasticity. The same area was stimulated by Barwood et al. (2013) using rTMS at resting motor threshold, revealing that rTMS modulates neural language networks and measures lexical-semantic function in patients with non-fluent aphasia. Another study by the same authors, applying rTMS to the anterior portion of the pars triangularis (Brodmann's area 45) in Broca's area in the right hemisphere, confirmed these findings, demonstrating that rTMS modulates neural language networks and

Table 2
Shows the principal studies concerning nibs applied to language and speech abilities.

Studies	Study design	Sample size	Intervention	Type and Areas of NIBS, domains	Type of stroke Disease duration	Outcomes	Adverse events	Major findings	PEDro score
Allendorfer et al. (2021)	RCT	24	EG: iTBS (Tx123; dosing strategies: 1-week iTBS with 2 weeks sham, 2 weeks iTBS with 1 week sham, or 3 weeks iTBS) CG: 3 weeks sham (Tx0)	iTBS IFG	single ischemic left middle cerebral artery stroke ≥ 1 year prior to enrollment	AQ BNT VPAT fMRI VGT	Not reported	iTBS-induced language improvements. Furthermore, there are associations were found between delayed fMRI changes and improvements in aphasia	7
Szaflarski et al. (2021)	RCT	28	GO: 3 weeks of sham G1: 1 week of iTBS/2 weeks of sham G2: 2 weeks of iTBS/1 week of sham G3: 3 weeks of iTBS	iTBS left frontal lobe	1 year after a single left, middle cerebral artery ischemic stroke	BNT SFT WAB-R AQ COWAT	adverse effects from rTMS, headachemuscle twitches residual local hypersensitivity	iTBS applied to the ipsilesional hemisphere can improve aphasia and result in cortical plasticity.	10
Barwood et al. (2011)	RCT	12	G1: Low frequency, 1 Hz rTMS for 20 min per day (1200 pulses), for 2 weeks (10 sessions) at 90 % of rMT G2: placebo TMS (using a SHAM coil)	rTMS rMT anterior portion of the Broca's area	ischemic hemorrhagic stroke ≥ 1 year after onset	BDAE BNT	Not reported	rTMS modulates neural language networks and measures lexical-semantic function in participants with non-fluent aphasia.	8
Barwood et al. (2013)	RCT	12	Low frequency (1 Hz) rTMS and six placebo patients for 20 min per day over 10 days	rTMS anterior portion of the pars triangularis in Broca's area (right hemisphere)	ischemic hemorrhagic stroke ≥ 1 year after onset	BDAE BNT	Not reported	rTMS modulates neural language networks and measures lexical-semantic function in participants with non-fluent aphasia	8
Lin et al. (2022)	RCT	33	real 1-Hz rTMS or sham stimulation (placebo coil delivered < 5 % of magnetic output with similar audible click-on discharge) for 10 consecutive week days	rTMS contralesional pars triangularis nonfluent aphasia	a first ischemic stroke at least 3 months after stroke onset	Resting-state fMRI CCAT	Not reported	rTMS improves language functions in terms of comprehension and expression ability compared to the sham group	9
Wang et al. (2014)	RCT	45	synchronous picture-naming training together with contralesional 1 Hz-rTMS for 10 daily sessions. The rTMS sham group received concurrent naming task along with the sham 1 Hz-rTMS	RTMS + ST contralesional pars triangularis nonfluent aphasia	first left middle cerebral artery infarction > 6 months	CCAT PNT	Not reported	The rTMS protocol and language training can be combined to achieve greater results than if used separately.	10
Hara et al. (2017)	Clinic study	8	11-day program of1-Hz rTMS	rTMS + ST IGF	ischemic hemorrhagic stroke ≥ 6	SLTA	Not reported	rTMS therapy and ST induced a significant	4

(continued on next page)

Table 2 (*continued*)

Studies	Study design	Sample size	Intervention	Type and Areas of NIBS, domains	Type of stroke	Outcomes	Adverse events	Major findings	PEDro score
					Disease duration				
					mounths after onset			improvement in language function	
Abo et al. (2012)	Clinic study	24	10 treatment sessions consisting of 40-min 1-Hz rTMS and 60-min ST	rTMS IGF for nonfluent aphasia and STG for fluent aphasia	cerebral infarction intracerebral hemorrhage in the left hemisphere ≥ 6 mounths after onset	auditory comprehension, reading comprehension repetition	general fatigue, headachenausea, epilepsy deterioration of language function	fMRI with aphasic type-based therapeutic LF-rTMS/intensive ST for chronic aphasia seems feasible and a useful neurorehabilitative protocol.	3
Chieffo et al. (2014)	RCT	5	3 sessions of rTMS: excitatory (10 Hz), inhibitory (1 Hz), and sham rTMS, in random sequence and separated by at least 1 week	rTMS right IFG Non fluent aphasia	first-ever stroke involving the left hemisphere ≥ 6 mounths after onset	Snodgrass naming test	Not reported	rTMS significantly improves naming in poststroke aphasic patients	10
Georgiou et al., (2022)	Clinical Study	6	1 Hz rTMS, and the remaining three were treated with cTBS	rTMS + cTBS right pars triangularis	single left hemisphere stroke at least six months	BDAE-SF PPVT-R GOAT MAIN RCPM SAQOL-39	any side effects	TMS has the potential to improve neuroplastic changes and facilitate speech recovery	10
Goh et al. (2015)	RCT	10	1 session of rTMS 5-Hz rTMS (total of 1200 stimuli) and 1 session of tDCS (1 mA of direct current) with 1 week between sessions.	rTMS tDCS rTMS: ipsilesional primary motor cortex (M1). anodal tDCS: ipsilesional M1	Left stroke ischemic hemorrhagic stroke ≥ 6 mounths after onset	MEP	any adverse events or side effects.	Both 5 Hz rTMS and anodal tDCS significantly increased corticospinal excitability for 30–60 min after stimulation. No statistically significant difference was found between the 2 stimulation techniques in their effects on MEP	5
Pestalozzi et al. (2018)	RCT	14	anodal tDCS sham-tDCS	tDCS left DLPFC	Left stroke ischemic hemorrhagic stroke ≥ 6 mounths after onset	PNT PFT RT	Headache neck pain, burning sensation on the skin, itching, redness of the skin, difficulties in concentrating, change in mood.	tDCS can improve lexical retrieval processing circuits	7
Richardson et al. (2015)	RCT	8	conventional tDCS and High Definition –tDCS + Computerized anomia treatment	High Definition –tDCS	Left stroke ischemic hemorrhagic stroke post-stroke onset was 9 to 312 months	Cool Edit Pro Version 2.0	No adverse events	HD-tDCS is acceptable for patients and doctors.	8
Baker et al. (2010)	RCT	10	5 days of anodal tDCS (1 mA for 20 min) and 5 days of sham tDCS (for 20 min, order randomized)	tDCS the left frontal cortex Naming accuracy	Left stroke ischemic hemorrhagic stroke post-stroke onset was 10 to 242 months	The untreated word lists	no significant adverse effects	Anodal tDCS + computerized treatment can lead to enhanced naming accuracy	7
Woodhead et al. (2018)	RCT	21	34 h of iReadMore training and 11 stimulation sessions, anodal stimulation or sham stimulation	tDCS + 'iReadMore' Alexia	Left stroke ischemic hemorrhagic stroke post-stroke onset was 12 to 158 months	WRT WSM Sentence reading Text reading SART CDP	fatigue, headaches and skin irritation	'iReadMore' improves the ability to read the trained words, with good maintenance of the therapeutic effect. Anodic stimulation produced small facilitation of learning and generalized even to untrained items	10
Xie et al. (2022)	RCT	25	tACS via 5 electrodes in a 4	tACS	Left stroke ischemic hemorrhagic	ABC	Not Reported	tACS improves understanding of	6

(continued on next page)

Table 2 (*continued*)

Studies	Study design	Sample size	Intervention	Type and Areas of NIBS, domains	Type of stroke Disease duration	Outcomes	Adverse events	Major findings	PEDro score
			× 1 ring configuration		stroke ≥ 6 mounths after onset			impaired spoken language.	

*Aphasia Quotient of the Western Aphasia Battery-Revised (WAB-R AQ), Aphasia Quotient (AQ), Boston Diagnostic Aphasia Examination (BDAE), Boston Diagnostic Aphasic Examination (BDAE), Boston Naming Test (BNT), Cognitive Linguistic Quick Test19 (CLQT), Communication Disability Profile (CDP), Concise Chinese Aphasia Test (CCAT), Controlled Oral Word Association Test (COWAT), Greek Boston Diagnostic Aphasia Examination-Shortened Version (BDAE-SF), Greek Object and Action Test (GOAT), Inferior Frontal Gyrus (IGF), Intensive Speech Therapy (ST), Left Inferior Frontal Gyrus (IFG), Motor Evoked Potentials (MEP), Multilingual Assessment Instrument for Narratives (MAIN), Multi-modality Aphasia Therapy (M−MAT), Peabody Picture Vocabulary Test–Revised (PPVT-R), Phonemic Fluency Task (PFT), Picture-Naming Test (PNT), Raven's Coloured Progressive Matrices (RCPM), resting Motor Threshold (rMT), Repetition Task (RT), Semantic Fluency Test (SFT), Standard Language Test of Aphasia (SLTA), Stroke and Aphasia Quality of Life Scale-39 Item (SAQOL-39), Superior Temporal Gyrus (STG), Sustained Attention to Response Task (SART), Verb Generation Task (VGT), Verbal Paired Associates Task (VPAT), Word Reading Test (WRT), Written Semantic Matching (WSM).

measures lexical-semantic function in participants with non-fluent aphasia (Barwood et al., 2011). In line with these findings, Lin et al. (2022) demonstrated that in non-fluent patients, rTMS stimulation of the contralesional pars triangularis improves linguistic functions in terms of comprehension and expression ability compared to the sham group (Lin et al., 2022) Furthermore, Wang et al. stimulated the same area, conducting treatment in non-fluent patients using rTMS with language training, and observed that combining the therapies yielded better results than therapies performed separately (Wang et al., 2014). In this context, Hara et al. performed rTMS at 1 Hz plus intensive speech therapy, highlighting a significant improvement in language function (Hara et al., 2017).

On the other hand, Abo et al. (2012) demonstrated that rTMS is feasible and useful not only for patients with non-fluent aphasia but also for patients with fluent aphasia. The same area inferior frontal gyrus (IFG) was stimulated by Chieffo et al. (2014), showing that rTMS significantly improves naming abilities.

Moreover, some authors used rTMS in combination with other NIBS or devices (Georgiou et al., 2022; Goh et al., 2015; Pestalozzi et al., 2018; Richardson et al., 2015; Baker et al., 2010). Georgiou et al. (2022) implemented rTMS plus Theta Burst Stimulation (TBS) on the right pars triangularis, observing improvements in neuroplastic changes and speech recovery. Another study using both rTMS and anodal tDCS observed that techniques used separately significantly increased corticospinal excitability for 30–60 min after stimulation (Goh et al., 2015). Indeed, an RCT study by Pestalozzi et al. (2018), showed that tDCS can improve lexical retrieval processing circuits. Furthermore, some authors have shown that tDCS is very useful when combined with other types of training to improve language skills. Richardson et al. (2015) conducted a study on 8 patients who underwent HD-tDCS along with a Computerized anomia treatment, observing that the combined training was acceptable and effective for patients and doctors. Another study using the same computerized training with tDCS was conducted by Baker et al. (2010). The authors showed that anodal tDCS plus computerized treatment can lead to increased naming accuracy. In this vein, Woodhead et al. (2018) showed that computerized training improves the ability to read the trained words, and tDCS produced a facilitation of learning that generalized even to untrained items.

Finally, only Xie et al. (2022) conducted an RCT study using tACS, and they observed that tACS improves the comprehension of impaired spoken language.

Furthermore, we found that four studies out of nineteen reported some adverse events after NIBS, as showed in Table 2. In particular, the most reported by the patients were headache (Szaflarski et al., 2021; Woodhead et al., 2018; Abo et al., 2012; Pestalozzi et al., 2018), skin irritation (Pestalozzi et al., 2018; Abo et al., 2012) and a sensation of general fatigue (Woodhead et al., 2018; Abo et al., 2012). In addition, Abo et al. (2012), reported that an epilepsy deterioration after NIBS, related to the language function.

4. Discussion

To the best of our knowledge, this is the first systematic review investigating the role of NIBS in improving cognitive outcomes in chronic stroke patients. Indeed, other reviews have dealt more broadly with the use of NIBS in improving cognitive function in the general population (Chen et al., 2024) and other neurological/psychiatric individuals (Mattioli et al., 2024) or have focused on Alzheimer's Disease (Jiang, Ramasawmy, & Antal, 2024; Andrade et al., 2024) and Multiple Sclerosis (Ken et al., 2022). Moreover, in two recent systematic reviews on neuromodulation and post-stroke cognitive deficits, although the authors found positive results, they did not differentiate acute/subacute from chronic stroke patients (Yan et al, 2024; Wang et al. 2022).

Our results demonstrated that NIBS may be a potential tool in enhancing cognitive, emotional, and speech domains also in chronic stroke patients. In this work, we observed that while there is a dearth of studies on cognitive and emotional aspects, most of them are RCTs with a good control of the risk of bias. Regarding cognitive components, most studies have utilized tDCS stimulation (Lu et al., 2015; Farahmandi Najafabadi et al., 2022; Richard et al., 2022; Kolskår et al., 2021; Li et al., 2021; Shaker et al., 2018) especially in combination with computerized cognitive training (Lu et al., 2015; Farahmandi Najafabadi et al., 2022; Richard et al., 2022; Kolskår et al., 2021; Li et al., 2021) resulting in positive outcomes in global cognition, attention, concentration, and memory. Several authors have highlighted that computer (PC)-based rehabilitation tools could facilitate training in post-stroke patients (Morone et al., 2019; Sampanis et al., 2015; Yoo et al., 2015). These tools are based on repeated training in cognitive tasks and incorporate audio–video feedback to increase patient engagement. Additionally, PC-based rehabilitation tools are highly customizable and enable extended training, thereby enhancing brain plasticity. The selected studies demonstrate that in this process, tDCS can effectively improve learning and generalize to other untrained skills. This is also evident in language, where almost all studies employing tDCS combine computerized naming and lexical retrieval training, leading to positive patient outcomes (Pestalozzi et al., 2018; Richardson et al., 2015; Baker et al., 2010; Woodhead et al., 2018). The integration of rehabilitation programs with PC-NIBS represents a promising research area in post-stroke rehabilitation. This combination offers an innovative approach to enhancing **non-**motor and cognitive recovery in stroke patients (Pestalozzi et al., 2018; Richardson et al., 2015; Baker et al., 2010; Woodhead et al., 2018). Through non-invasive cortical stimulation paired with targeted rehabilitation activities, there is the potential to promote neural plasticity and improve **non-motor** and cognitive function. Furthermore, the adaptation of personalized treatment protocols, integration with emerging technologies, and exploration of combination therapies could contribute to optimizing the effectiveness of these programs and translating them into feasible clinical applications to improve the quality of life for post-stroke patients

(Pestalozzi et al., 2018; Richardson et al., 2015; Baker et al., 2010; Woodhead et al., 2018). As for rTMS, it is widely used as a standalone technique, although in some studies, it is combined with other approaches such as iTBS or computerized training (Yun et al., 2015; Allendorf et al., 2021; Szaflarski et al., 2021; Barwood et al., 2013; Lin et al., 2022; Wang et al., 2014; Hara et al., 2017; Abo et al., 2012; Chieffo et al., 2014; Georgiou et al., 2022; Goh et al., 2015; Pestalozzi et al., 2018; Richardson et al., 2015; Baker et al., 2010; Woodhead et al., 2018; Xie et al., 2022). Regardless of the method of application, rTMS has proven to be highly effective in enhancing cognitive, emotional, and language functions.

An interesting aspect concerns the areas stimulated. We observed that in most cognitive studies, the dlPFC is stimulated, while some studies also target the frontal and temporal cortex. To stimulate speech functions, the IFG and Broca's area are employed for non-fluent aphasia, and the superior frontal gyrus (SFG) is used for fluent aphasia. Frontal areas play a significant role in cognitive processes, and appropriate stimulation can enhance mental processes. Conversely, iTBS is used in only two studies, indicating that this method, when applied to the ipsilesional hemisphere, can improve aphasia and cortical plasticity (Yun et al., 2015; Allendorf et al., 2021).

In chronic stroke, maladaptive plasticity often occurs due to the imbalance between inhibitory and excitatory mechanisms, leading to persistent functional deficits. This maladaptive plasticity can involve cortical reorganization characterized by abnormal neural network activation and synaptic connectivity. In fact, some authors have highlighted alterations in neural excitability following cerebral stroke, with similarity between EEG activity during sleep and EEG activity after stroke (Russo et al., 2023; Viganò et al., 2023). Russo et al. (2023) demonstrated that while awake, stroke patients exhibit slow waves like those present during Non-REM Sleep. Therefore, differentiating the type of cortical activation detected via EEG and relating it to NIBS could promote greater brain plasticity. NIBS techniques, such as TMS and tDCS, modulate cortical excitability and synaptic plasticity by targeting specific brain regions. NIBS promotes neuroplasticity through mechanisms such as long-term potentiation and long-term depression, facilitating synaptic strengthening or weakening, respectively (Xu et al., 2022; Naro et al., 2016).

Despite its potential therapeutic benefits, NIBS interventions may be associated with adverse events such as mild discomfort, headache, and transient changes in mood or cognition (Lu et al., 2015; Allendorf et al., 2021; Abo et al., 2012; Pestalozzi et al., 2018; Woodhead et al., 2018). Understanding the neurophysiological mechanisms of NIBS and monitoring for adverse events is essential for optimizing treatment outcomes and ensuring patient safety in clinical practice. In this sense, further studies are needed to provide direct evidence of the efficacy of NIBS to prevent the development of maladaptive plasticity at an early stage. Indeed, it could be useful to validate outcomes related to neuroplasticity using TMS, high density electroencephalography, and neuroimaging techniques and correlating them with functional and structural maladaptive plastic changes with clinical outcomes (Naro et al., 2016). Moreover, future studies should manage some challenges like understanding the right dose and duration of NIBS and how to tailor the rehabilitation protocol according to the pathology and patient's characteristics (Bonanno and Calabrò, 2023; Guerra et al., 2020).

The lack of studies on emotional/psychological components is surprising. In the literature, we only found one study on depression in post-stroke patients and one on apathy. Since emotional symptoms are prevalent in post-stroke patients, future research could investigate this critical issue.

Although the selected studies are consistent in terms of the areas stimulated, the methods employed, and the evaluation of outcomes, we observed some critical issues and limitations. First, samples often consist of a limited number of patients, making it challenging to generalize the results. Second, there is often a lack of follow-up assessments to demonstrate the long-term maintenance of results; then, we are not able to state whether and to which extent the NIBS effect lasts. last. Also, we used a mixed approach, and we did not evaluate the effects of rTMS and tDCS separately. Another significant limitation of this review is the lack of an in-depth analysis of the significance of the findings and the real-world impact of the observed changes, such as CMID or QoL. It is important to note that our review is not based on a *meta*-analysis but rather on a qualitative synthesis of the available literature. Additionally, we did not assess the adequacy of outcome metrics as these were not consistently reported across the included studies. Finally, there is scarce evidence regarding the effectiveness of NIBS on emotional components after chronic stroke, and studies on cognitive domains are also scarce. Therefore, future studies should aim to increase sample sizes, encourage longer follow-ups, and include a broader range of symptoms in the evaluation of patients' cognitive and emotional outcomes.

To sum up, the findings emerging from our review have important clinical implications for the treatment of patients with chronic stroke. In particular, the demonstrated effectiveness and safety of NIBS, such as tDCS, in improving cognitive and language functions suggests that this approach could be successfully integrated into post-stroke rehabilitation programs. Indeed, the use of PC-based rehabilitation tools combined with NIBS could provide an opportunity to improve the effectiveness of cognitive and language recovery in chronic stroke patients. However, it is important to acknowledge that there are still limitations in current research, including the need for studies with larger sample sizes and long-term follow-up to evaluate the maintenance of results over time. Further research is needed to evaluate the effectiveness of NIBS on emotional and psychological components after chronic stroke, as well as to address challenges related to personalizing treatment protocols and optimizing stimulation doses. Therefore, future research should focus on expanding knowledge about the mechanisms of action of NIBS and identifying strategies to maximize its efficacy in the treatment of chronic stroke.

In conclusion, our findings underscore the potential of NIBS, such as tDCS and rTMS, in the cognitive, linguistic, and emotional recovery of post-stroke patients. Although it seems that NIBS may work as a complementary tool to enhance cognitive and communication abilities in patients with stroke –also in the chronic phase- evidence on behavioural outcomes is still poor. Future studies should focus on this important issue to confirm the effectiveness of neuromodulation in chronic neurological diseases, including stroke, and to understand if and to which extent its aftereffects lasts.

5. Institutional Review Board Statement

Not applicable.

6. Informed Consent Statement

Not applicable.

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CRediT authorship contribution statement

Maria Grazia Maggio: Writing – review & editing, Writing – original draft, Validation, Data curation, Conceptualization. **Mirjam Bonanno:** Writing – original draft, Visualization, Conceptualization. **Serena Filoni:** Writing – review & editing. **Irene Ciancarelli:** Writing – review & editing. **Angelo Quartarone:** Supervision, Resources. **Rocco Salvatore Calabrò:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Methodology.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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