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Review

Transcranial direct current stimulation in post-stroke aphasia rehabilitation: A systematic review

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ABSTRACT

Background: Transcranial direct current stimulation (tDCS) is a non-invasive tool that induces neuromodulation in the brain. Several studies have shown the effectiveness of tDCS in improving language recovery in post-stroke aphasia. However, this innovative technique is not currently used in routine speech and language therapy (SLT) practice.
Objective: This systematic review aimed to summarise the role of tDCS in aphasia rehabilitation.
Methods: We searched MEDLINE via PubMed and Scopus on October 5, 2018 for English articles published from 1996 to 2018. Eligible studies involved post-stroke aphasia rehabilitation with tDCS combined or not with SLT.
Results: We retained 5 meta-analyses and 48 studies. Among the 48 studies, 39 were randomised controlled trials (558 patients), 2 prospective studies (56 patients), and 5 case studies (5 patients). Two articles were sub-analyses of a randomised clinical trial. Methods used in these studies were heterogeneous. Only 6 studies did not find a significant effect of tDCS on language performance. As compared with earlier meta-analyses, the 2 latest found significant effects.
Conclusion: Evidence from published peer reviewed literature is effective for post-stroke aphasia rehabilitation at the chronic stages. tDCS devices are easy to use, safe and inexpensive. They can be used in routine clinical practice by speech therapists for aphasia rehabilitation. However, further studies should investigate the effectiveness in the subacute post-stroke phase and determine the effect of the lesion for precisely identifying the targeted brain areas. We discuss crucial challenges for future studies.

1. Introduction

About one third of all stroke patients are affected by language problems, collectively referred to as aphasia [1,2]. Aphasia affects functional outcome, mood, quality of life, participation restrictions and the ability to return to work [3–5].

Recovery from aphasia is driven in part by spontaneous neuroplasticity mechanisms (i.e., brain structural and functional changes). These mechanisms can be enhanced by rehabilitation [6]; speech and language therapy (SLT) remains the gold standard [7,8]. In addition to demographic predictors of recovery (for a review, see Watila et Balarabe, 2015 [9]), linguistic factors [10,11] or lesion-related factors contribute to the recovery from aphasia. Involvement of perilesional left-hemisphere regions in linguistic tasks and/or the (possibly maladaptive) activation of the non-dominant hemisphere can have a positive or negative effect on neuroplasticity and thus affect recovery (for a review, see Hartwigsen and Saur, 2017 [12]). Indeed, lesions of the left hemisphere might provide cortical disinhibition in perilesional structures, thereby increasing activity in left areas involved in language, with this perilesional activation associated with good recovery [13,14]. However, this lesion can also disrupt the balance of inter-hemispheric competition.

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The healthy brain features mutual inhibitory control between the 2 hemispheres, mediated by transcallosal connections. A lesion induces decreased excitation in the left hemisphere, often associated with greater excitation in homologous contralateral areas [15] because of reduced transcallosal inhibition of the right hemisphere by the left one. However, the right hemisphere can still inhibit the left one, worsening hypoactivation in the damaged left areas [16]. This schematic model of inter-hemispheric imbalance could provide the rationale for neuromodulation (Fig. 1).

Recovery could be improved by modulating cortical activity in these left or right areas with promising non-invasive brain stimulation (NIBS) technologies such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). Usually, NIBS is used to increase cortical activity of the perilesional cortex, particularly targeting language areas in the left hemisphere (Broca's area, Wernicke's area or motor cortex), or to decrease activity of contralesional areas such as the right inferior frontal gyrus [17]. In post-stroke management, repetitive TMS (rTMS) has been successful in treating paresis, spasticity, neglect and dysphagia (for a review, see Lefaucheur et al., 2011) [18]. The first studies using rTMS in aphasia rehabilitation found a significant effect of 1-Hz inhibitory stimulation over the homolog of Broca's area in chronic aphasia [19,20]. These promising results were confirmed in many studies and randomised clinical trials.

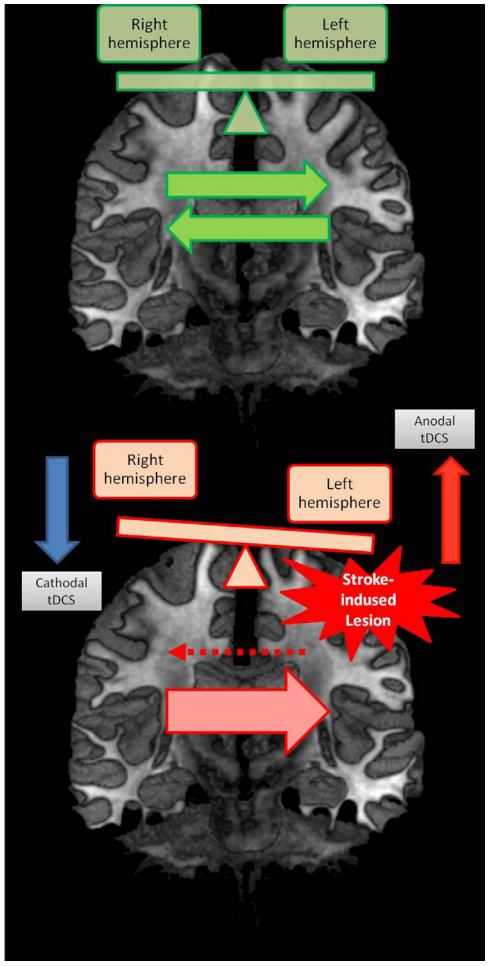

Fig. 1. Mutual inhibitory control between the 2 hemispheres and inter-hemispheric imbalance after stroke. Excitatory stimulation (anodal transcranial direct current stimulation [tDCS] or high-frequency repetitive transcranial magnetic stimulation [rTMS]) over the damaged hemisphere or inhibitory stimulation (cathodal tDCS or low-frequency rTMS) over the contralesional hemisphere could theoretically improve post-stroke symptoms by reducing this imbalance.

Thiel et al. showed a significant effect of this inhibitory stimulation over the right pars triangularis as compared with sham stimulation in patients after subacute stroke and aphasia [21]. The same significant effects were found in patients with chronic aphasia [22]. Dual stimulation (i.e., right inhibition and left facilitation of the right homologous and left Broca's area, respectively) had significant positive effects on language performance in subacute aphasia [23]. A recent study suggested that low-frequency rTMS over the right homologous Broca's area and high-frequency rTMS over the left area were both beneficial and that a low frequency may have immediate benefits that persist long-term, whereas high-frequency rTMS may have only long-term benefits [24]. rTMS allows for focal modulations and accurate spatial resolution. However, because of methodologic constraints (risks and contraindications, cost, noise, size of the device, etc.), this tool cannot be easily used for on-line rehabilitation (i.e., SLT during stimulation), so its use in routine clinical care is limited.

Contrary to rTMS, tDCS seems the most relevant tool in these cases. Indeed, the technique is inexpensive, quick, easy-to-use and safe, with very few contraindications, and is small and portable, so it is convenient for routine clinical practice in SLT [17,25]. tDCS works by inducing electrical current flow to the scalp by means of 2 electrodes, for usually up to 10 to 30 min. In the motor cortex, anodal tDCS has been found to increase excitability of the underlying cortex, with cathodal tDCS decreasing the excitability [26].

tDCS has had positive effects on aphasia rehabilitation. This systematic review aimed to summarise the effect of tDCS on aphasia rehabilitation.

2. Methods

This systematic review followed PRISMA guidelines (www.prisma-statement.org). We searched MEDLINE via PubMed and Scopus on October 5, 2018 for English articles published from 1996 to 2018 by using the following keywords in titles, abstracts and keywords: "aphasia" AND "Transcranial direct current stimulation" OR "tDCS". Eligible studies involved post-stroke aphasia rehabilitation with tDCS combined or not with SLT. We excluded articles concerning primary progressive aphasia, rTMS, other neuromodulation tools or studies focusing only on the effects of tDCS in healthy subjects and also literature reviews, but studies within these reviews were assessed to complete our research. Meta-analyses were considered to describe sub-analyses exploring various procedures (e.g., frequency and a possible dose-dependent effect or subacute versus chronic post-stroke phase). Two authors (EB, BG) assessed the eligibility of articles. Consensus was achieved with discussion or consultation with a third author (HC).

3. Results

On October 5, 2018, after removal of duplicates, 177 articles were retrieved from the literature search. The flow of articles in the study is in Fig. 2. We included reports of 5 meta-analyses and 48 studies on post-stroke aphasia and tDCS. Among the 48 studies, 39 were randomised controlled trials (558 patients), 2 prospective studies (56 patients), and 5 case studies (5 patients). Finally, 2 articles were sub-analyses of a randomised clinical trial. Tables 1–3 synthesises the articles analysed.

The 39 studies used heterogeneous methods regarding targeted areas, intensity and polarity of stimulation, duration, and frequency, etc. (Tables 1 and 4). No studies reported a negative effect of tDCS on aphasic patients. Two of these studies [47,48] were sub-analyses of the same clinical trial [46]. Among the 39 randomised clinical trials, six did not find a significant effect of

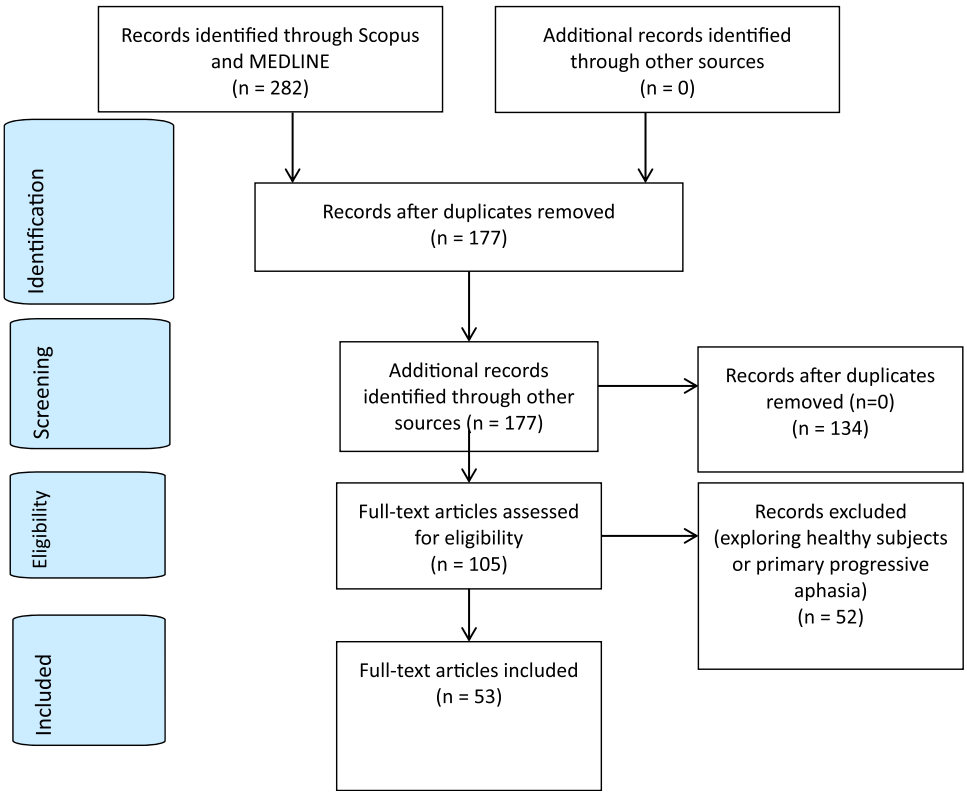

Fig. 2. Flow of articles in the study.

the use of tDCS on language performance [32,34,35,42,65,66]; 2 used off-line tDCS (i.e., stimulation at rest, not combined with any language task [32,42]), 3 used off-line tDCS after SLT in post-acute aphasia [34,35,65], and one used anodal tDCS over LIFG combined with word-finding therapy but in a subacute phase [66].

3.1. Prospective studies and case reports

The 2 prospective studies and 5 case reports are detailed in Tables 2 and 5. All studies found a significant effect of tDCS combined with SLT and used the same heterogeneous methods as clinical trials.

3.2. Meta-analyses

Five meta-analyses aggregated results from several studies; the outcome for all these studies was performance in naming (Table 3). The first 3 meta-analyses did not find significant effects [74–76] in contrast to the latest ones [77,78]. In 2013, in a first meta-analysis aggregating 5 studies and 54 patients, Elsner et al. [75] did not find effectiveness regarding the relative change in naming tests, and the same team, aggregating 6 studies and 66 participants, had the same conclusion 2 years later [74]. A meta-analysis aggregating 3 studies and 32 patients and focusing on inhibition of the right hemisphere by using rTMS or tDCS did not find a significant effectiveness of cathodal tDCS on the right hemisphere but found a significant global effect when including all studies that used rTMS or tDCS [76]. Another meta-analysis [77], aggregating 8 studies with 140 patients and focusing on both rTMS and tDCS, found tDCS significantly effective in chronic patients but no effect during subacute stages. A recent meta-analysis [78] explored repetitive sessions of tDCS and found a significant dose-dependent effect. Moreover, the difference between active and sham stimulation was greater after anodal than cathodal tDCS and left than right hemisphere stimulation was particularly efficient when the active electrode targeted the left temporo-parietal versus left frontal lobe. However, the authors found no significant interaction between side and location or polarity and location.

3.3. tDCS montage: anodal versus cathodal stimulation/brain areas

To enhance language production, 19 studies stimulated the left inferior frontal gyrus (LIFG), corresponding to Broca's area, with anodal tDCS combined with various language production tasks. Indeed, combining anodal tDCS over LIFG with repetition tasks (syllables and word repetition) improved accuracy in speech production [30], the naming task improved naming accuracy [31,37] and conversational therapy improved picture naming, noun and verb naming [38]. It also allowed for a more informative and cohesive speech with more content units, verbs and sentences [33,36] and improved reading ability [45]. The effect of melodic intonation therapy (MIT), known to improve speech fluency for very non-fluent patients, seemed enhanced when targeting contralesional areas with excitatory stimulation (i.e., anodal tDCS on the right inferior frontal gyrus [RIFG]) [54,58]. For other specific areas such as temporo-parietal areas, cathodal stimulation over the right homologous Wernicke's area or anodal stimulation over the left Wernicke's area improved auditory verbal comprehension [53], and anodal stimulation over the left posterior perisylvian region also improved auditory comprehension [39]. Anodal stimulation of the left dorsolateral prefrontal cortex improved verbal fluency [49]. Moreover, modulation of several uncommon areas was recently explored in aphasic patients. Indeed, recent studies have focused on cerebellar stimulation in post-stroke aphasia: anodal tDCS over the right cerebellum improved spelling of words [72] and cathodal tDCS over the right cerebellum

Table 1
Design and main results of randomised clinical trials. Details of the procedures are in Table 4.

Study (design)	No. of patients, stage (time since stroke) and type of aphasia	Stimulation parameters: polarity, location, intensity and duration	No. of sessions and task combined with tDCS	Results
Anodal targeting the left hemisphere				
Baker et al., 2010 [27] (crossover, double-blinded vs sham)	10 Chronic (>10 months) 6 fluent and 4 non-fluent	Anodal: left frontal cortex (individualised determination of electrode placement using fMRI) 1 mA, 20 min	5 sessions Computerised anomia treatment	Improvement in naming accuracy just after tDCS and 1 week after tDCS
Fiori et al., 2011 [28] (crossover, double-blinded vs sham)	3 Chronic (>6 months) non-fluent	Anodal: left Wernicke's area 1 mA, 20 min	5 sessions Picture-naming task	Improvement in naming accuracy and shorter naming latencies after tDCS and 3 weeks after tDCS
Fridriksson et al., 2011 [29] (crossover, double-blinded vs sham)	8 Chronic (>10 months) Fluent with posterior cortical or sub-cortical lesions	Anodal: left posterior cortex (individualised determination of electrode placement by fMRI) 1 mA, 20 min	5 sessions Computerised anomia treatment	Reduction of reaction-time naming of trained items immediately post-treatment and 3 weeks later
Marangolo et al., 2011 [30] (crossover, double-blinded vs sham)	3 Chronic (>21 months) non-fluent	Anodal: LIFG 1 mA, 20 min	5 sessions Repetition task	Better accuracy in speech production: syllables and words repetition. Improvement in other language test: reading, writing, at post-treatment and 2 months after
Marangolo et al., 2013 [31] (crossover, double-blinded vs sham)	7 Chronic (>6 months) non-fluent	Anodal: left Broca's area or Anodal: left Wernicke's area 1 mA, 20 min	5 sessions Naming task (nouns and verbs)	Improvement in verb naming after anodal tDCS over Broca's area, improvement in noun naming after anodal tDCS over Wernicke's area, at post-treatment and 1 month after
Volpato et al., 2013 [32] (crossover, double-blinded vs sham)	8 Chronic (>6 months) 6 fluent and 2 non-fluent	Anodal: LIFG 2 mA, 20 min	10 sessions No task (off-line tDCS)	No significant effect of off-line tDCS (except for 1 patient: improvement in action naming task)
Marangolo et al., 2013 [33] (crossover, double-blinded vs sham)	12 Chronic (>14 months) non-fluent	Anodal: left Broca's area or Anodal: left Wernicke's area 1 mA, 20 min	10 sessions Conversational therapy (spontaneous conversation about videoclips)	More informative speech: more content units, verbs and sentences, at post-treatment and at 1-month follow-up after anodal tDCS over Broca's area
Polanowska et al., 2013 [34] (crossover, double-blinded vs sham)	24 Post-acute (2–24 weeks) non-fluent	Anodal: LIFG 1 mA, 10 min	15 sessions 45 min of SLT after stimulation (off-line tDCS)	Improvement in naming accuracy in both groups (A-tDCS and sham), higher effect sizes in naming time for A-tDCS at post-treatment and at 3-month follow-up
Polanowska et al., 2013 [35] (crossover, double-blinded vs sham)	37 Post-acute (2–24 weeks) 13 fluent and 24 non-fluent	Anodal: LIFG 1 mA, 10 min	15 sessions 45 min of SLT after stimulation (off-line tDCS)	Improvement in all items of BDAE but no significant difference between the 2 groups (A-tDCS and sham) at post-treatment and at 3-month follow-up
Marangolo et al., 2014 [36] (crossover, double-blinded vs sham)	8 Chronic (>14 months) non-fluent	Anodal: LIFG or Anodal: left Wernicke's area 1 mA, 20 min	10 sessions Conversation therapy (spontaneous conversation about videoclips)	After A-tDCS over LIFG, better abilities to produce cohesive speech: pronouns, ellipses, word repetitions, conjunctions
Vestito et al., 2014 [37] (crossover, single-blinded vs sham)	3 Chronic (>20 months) non-fluent	Anodal: LIFG 1.5 mA, 20 min	10 sessions Naming training	Improvement in naming performance up to 16 weeks after stimulation.
Campana et al., 2015 [38] (crossover, double-blinded vs sham)	20 Chronic (>6 months) non-fluent	Anodal: LIFG 2 mA, 20 min	10 sessions Conversational therapy (1 hr)	Improvement in picture description, noun and verb naming
Wu et al., 2015 [39] (blinded vs sham)	12 Post-subacute (3–6 months after stroke) 8 Broca's, 2 mixed, 1 anomic, 1 conductive	Anodal: left posterior perisylvian region 1.2 mA, 20 min	20 sessions Picture-naming and auditory word-picture identification	Improvement in picture-naming and in auditory comprehension
Meinzer et al., 2016 [40] (crossover, double-blinded vs sham)	26 Chronic (>15 months) 9 Broca's, 9 Wernicke's, 6 Global, 2 Amnestic	Anodal: left primary motor cortex 1 mA, 20 min	8 sessions Computer-assisted naming treatment (3 hr per day)	Improvement in naming ability for trained and untrained items, generalization to everyday communication, at post-treatment and at 6-month follow-up

Table 1 (*Continued*)

Study (design)	No. of patients, stage (time since stroke) and type of aphasia	Stimulation parameters: polarity, location, intensity and duration	No. of sessions and task combined with tDCS	Results
Branscheidt et al., 2017 [41] (crossover, double-blinded vs sham)	16 Chronic (>3 months) non-fluent	Anodal: left primary motor cortex (individualised determination of electrode placement by TMS) 2 mA, 20 min	2 sessions Lexical decision task (words/ pseudowords)	Improvement in overall accuracy in lexical decision task, especially lexical decision of action words
Santos et al., 2017 [42] (crossover, double-blinded vs sham)	13 Chronic (>6 months) 7 Anomic, 6 Broca's	Anodal: LIFG 2 mA, 20 min	1 session No task (off-line tDCS)	No effect on naming task
Spielmann et al., 2018a [43] (crossover, double-blinded vs sham)	58 Subacute (3 weeks to 3 months) 30 fluent, 20 non-fluent, 8 mixed	Anodal: LIFG 1 mA, 20 min	5 sessions Word-finding therapy (45 min)	No significant differences between anodal tDCS and sham-tDCS on the Boston Naming Test at 6-month follow-up
Spielmann et al., 2018b [44] (crossover, double-blinded vs sham)	13 Chronic	Anodal: LIFG or LSTG 1 mA, 20 min	1 session for each of the 3 conditions Word-finding therapy (30 min)	Improvement in naming ability for trained items in the LIFG condition compared with the other conditions
Woodhead et al., 2018 [45] (crossover, double-blinded vs sham)	21 Chronic patients with alexia	Anodal: LIFG 2 mA, 20 min	11 stimulation sessions combined with face-to-face reading therapy using a digital application + at least 35 h of reading therapy alone	Improvement in reading ability. tDCS permitted a small facilitation of learning and generalisation to untrained items No significant changes at the sentence or text reading level
Fridriksson et al., 2018 [46] (double-blinded vs sham, futility design, intent-to-treat analysis)	74 Chronic	Anodal: left temporo-parietal regions (individualised determination of electrode placement by fMRI) 1 mA, 20 min	15 sessions Computerised anomia treatment (matching pictures task, 45 min)	Improvement in naming task, failure to reject the null hypothesis (i.e., A-tDCS led to at least a 1.5-item greater improvement in correct naming compared with sham stimulation) No evidence of an interaction of treatment over time at 24 weeks after treatment [47] Analysis of BDNF genotype (66 patients) showed that patients with typical BDNF tended have milder symptoms and better improvement induced by anodal tDCS [48]
Pestalozzi et al., 2018 [49] (crossover, double-blinded vs sham)	14 chronic	Anodal: left DLPFC 2 mA, 20 min	1 session Picture naming, repetition, phonemic fluency	Improvement in verbal fluency as well as in the speed of naming high-frequency words, but not in word repetition
Other target and/or polarity				
Monti et al., 2008 [50] (crossover, double-blinded vs sham)	8 Chronic non-fluent	Anodal or cathodal: left Broca's area or occipital area 2 mA, 10 min	1 session Picture naming task	Improvement in accuracy of the picture naming task 1 min after cathodal tDCS over Broca's area
Kang et al., 2011 [51] (crossover, double-blinded vs sham)	10 Chronic (>6 months) 4 Broca's, 3 global, 2 anomic, 1 transcortical motor	Cathodal: Right Broca's homolog area 2 mA, 20 min	5 sessions World retrieval training	Improvement in naming accuracy at 1 hr after the last tDCS treatment session
Floel et al., 2011 [52] (crossover, double-blinded vs sham)	12 Chronic 9 non-fluent and 3 fluent	Anodal or cathodal: Right temporo-parietal cortex 1 mA, 20 min	3 sessions High-frequency anomia training on computer (2 hr per day)	Improvement in naming accuracy after a-tDCS and 2 weeks later
You et al., 2011 [53] (crossover, double-blinded vs sham)	21 Subacute (16–38 days) non-fluent	Cathodal: right Wernicke's area or Anodal: left Wernicke's area 2 mA, 30 min	10 sessions Conventional SLT	Improvement in auditory verbal comprehension at post-treatment, more in patients treated with a cathodal tDCS
Vines et al., 2011 [54] (crossover, double-blinded vs sham)	6 Chronic (>15 months) non-fluent	Anodal: RIFG 1.2 mA, 20 min	3 sessions MIT	Improvement in fluency of speech at post-treatment
Marangolo et al., 2013 [55] (crossover, double-blinded vs sham)	8 Chronic (>6 months) non-fluent	Anodal: LIFG Cathodal: RIFG (bihemispheric stimulation) 2 mA, 20 min	10 sessions Language therapy for apraxia of speech	Better accuracy and speed in articulating, improvement in picture description, noun and verb naming, word repetition, reading, at post-treatment and at 1-week follow-up

Table 1 (*Continued*)

Study (design)	No. of patients, stage (time since stroke) and type of aphasia	Stimulation parameters: polarity, location, intensity and duration	No. of sessions and task combined with tDCS	Results
Lee et al., 2013 [56] (crossover, double-blind, single vs dual tDCS)	11 Chronic (>8 months) 6 non-fluent and 5 fluent	Anodal: LIFG (single tDCS) or Anodal: LIFG Cathodal: RIFG (dual stimulation) 2 mA, 30 min	1 session SLT in the last 15 min	Improvement in naming accuracy in both groups (single tDCS and dual tDCS), improvement in the response time in the dual tDCS group
Marangolo et al., 2014 [57] (crossover, double-blinded vs sham)	7 Chronic (>6 months) non-fluent	Anodal: LIFG Cathodal: RIFG (bihemispheric stimulation) 2 mA, 20 min	10 sessions 90 min of daily language treatment by a pragmatic approach	Improvement in picture description, noun and verb naming at post-treatment and 1 week after
Cipollari et al., 2015 [58] (crossover, double-blinded vs sham)	6 Chronic (>10 months) non-fluent	Anodal: RIFG 2 mA, 20 min	15 sessions MIT	Improvement in speech fluency: better accuracy for words and sentences for treated and untreated items, at post-treatment and 1 week after
Shah-Basak et al., 2015 [59] (crossover, double-blinded vs sham)	12 Chronic (>7 months) non-fluent	Anodal: left frontal lobe or Anodal: right frontal lobe or Cathodal: left frontal lobe or Cathodal: right frontal lobe 2 mA, 20 min	10 sessions Picture naming task	Greatest improvement in naming with left cathodal stimulation at 2-week and 2-month follow-up
de Aguiar et al., 2015 [60] (crossover, double-blinded vs sham)	9 Chronic (>8 months) 3 fluent, 6 non-fluent	Anodal and cathodal: left perilesional area (individualised determination of electrode placement by MRI) 1 mA, 20 min	10 sessions SLT based on ACTION treatment (1 hr)	Improvement in verb production, with generalization to untreated items
Marangolo et al., 2016 [61] (crossover, double-blinded vs sham)	9 Chronic (>7 months) non-fluent	Anodal: LIFG Cathodal: RIFG (bihemispheric stimulation) 2 mA, 20 min	15 sessions SLT focused on articulatory disorders (syllables and words repetition)	Improvement in speech articulation: better accuracy in articulating treated and untreated stimuli
Norise et al., 2017 [62] (crossover, double-blinded vs sham)	9 Chronic (>8 months) non-fluent	Anodal: left frontal lobe or Anodal: right frontal lobe or Cathodal: left frontal lobe or Cathodal: right frontal lobe 2 mA, 20 min	10 sessions Picture naming task	Fluency improvements: word-level and sentence level, grammatical accuracy, and lexical selection. Better improvement at 2 weeks follow-up when the baseline language is severe
Marangolo et al., 2017 [63] (crossover, double-blinded vs sham)	12 Chronic (>14 months) non-fluent	Cathodal: right cerebellum (c-tDCS) 2 mA, 20 min	5 sessions Language treatment for verb improvement	Improvement in verb generation (but no effect on verb naming) after treatment and 1 week after
Marangolo et al., 2017 [64] (crossover, double-blinded vs sham)	14 Chronic (>18 months) non-fluent	Anodal: 10th thoracic spinal vertebrae (tsDCS) 2 mA, 20 min	5 sessions Verb and noun naming task	Improvement in verb naming (but no noun naming) at post-treatment and 1 week after
Silva et al., 2018 [65] (double-blinded vs sham)	14 Chronic (>3months) non-fluent aphasia	Cathodal: Right Broca's-homolog area 2 mA, 20 min	5 sessions No task (off-line tDCS)	No significant differences between active-tDCS and sham-tDCS at the Boston or Snodgrass Naming Test at 1-week follow-up

BDAE: Boston Diagnostic Aphasia Examination; BDNF: brain-derived neurotrophic factor; DLPFC: dorsolateral prefrontal cortex; FMRI: functional MRI; LIFG: left inferior frontal gyrus; LSTG: left superior temporal gyrus; MIT: melodic intonation therapy; RIFG: right inferior frontal gyrus; SLT: speech language therapy; TMS: transcranial magnetic stimulation.

Table 2
Design and main results of other studies or case reports. Details of the procedures are in Table 5.

Study (design)	No. of patients, stage (time since stroke) and type of aphasia	Stimulation parameters: polarity, location, intensity and duration	No. of sessions and task combined with tDCS	Results
Jung et al., 2011 [67] (retrospective study)	37 From early subacute stage (<30 days for 13 patients) to chronic (>90 days for 10 patients) 10 fluent 26 non-fluent	Cathodal: left Broadmann area 45 1 mA, 30 min	10 sessions Standard SLT	Improvement in each item of the Western Aphasia Battery: fluency, auditory comprehension, repetition, naming, reading, writing
Cherney et al., 2013 [68] (case report)	1 Chronic (204 months) non-fluent	Cathodal: right temporal area (determination of electrode placement by fMRI) 1 mA, 13 min	30 sessions 90 min of computer SLT	Improvement in Western Aphasia Battery Aphasia Quotient at post-treatment, improvement in auditory comprehension at 6 weeks follow-up
Santos et al., 2013 [69] (no control group, no blind)	19 Chronic (>6 months) 8 Broca's, 7 Anomic, 4 Mixed	Cathodal: right primary motor cortex 2 mA, 20 min	10 sessions No language task	Improvements in simple sentence comprehension, naming and verbal fluency (animals)
Galletta et al., 2015 [70] (crossover, double-blinded vs sham)	1 Chronic (20 months) fluent anomic	Anodal: LIFG 1 mA, 20 min	10 sessions SLT (noun and verb production in sentence context)	Improvement in verb production
Manenti et al., 2015 [71] (case report)	1 Chronic (8 months) non-fluent	Anodal: left dorsolateral prefrontal cortex Cathodal: right dorsolateral prefrontal cortex (bihemispheric stimulation) 2 mA, 25 min	20 sessions 25 min of verb anomia training (off-line tDCS)	Improvement in verb naming (treated and untreated verbs) at post-treatment and 48 weeks after
Sebastian et al., 2017 [72] (crossover, double-blinded vs sham)	1 Chronic (5 years after a second stroke) non-fluent	Anodal: right cerebellum (c-tDCS) 2 mA, 20 min	15 sessions Spelling treatment protocol (5 min)	Improvement in spelling for trained and untrained words, generalization to written picture naming immediately after and 2 months post-treatment
Sandars et al., 2018 [73] (case report)	1 Chronic (9 years post-stroke) Broca's	Anodal, cathodal, or sham stimulation of the LIFG and RIFG 1 mA, 20 min	18 sessions (3 for each condition) sessions of Computerised naming therapy for 20 min	Naming accuracy increased significantly more following perilesional anodal stimulation vs sham stimulation, and this effect remained significant at 3 weeks post-therapy

fMRI: functional MRI; LIFG: left inferior frontal gyrus; RIFG: right inferior frontal gyrus; SLT: speech language therapy.

Table 3
Main results of meta-analyses.

Meta-analysis	No. of patients, number of studies	Stimulation parameters for experimental groups	Outcome measure	Standardised mean difference and confidence interval	Conclusions
Elsner et al., 2013 [75]	54 patients, 5 studies	Anodal, cathodal, or both (bihemispheric)	Naming accuracy	SMD = 0.31; 95% CI: −0.26–0.87	No evidence that tDCS enhanced SLT outcomes. No adverse events
Elsner et al., 2015 [74]	66 patients, 6 studies	Anodal, cathodal, or both (bihemispheric)	Analysis based only on the Secondary outcome of the meta-analysis: Naming accuracy No study measuring the primary outcome: functional communication	SMD = 0.37, 95% CI: −0.18–0.92	No evidence of the effectiveness of tDCS versus control (sham tDCS) for improving functional communication, language impairment and cognition. No adverse events
Otal et al., 2015 [76] (exploring also rTMS effect)	32 patients, 3 studies	Cathodal over the non-lesioned hemisphere	Naming accuracy	SMD = 0.42, 95% CI: −0.29–1.13	No evidence of the effectiveness of cathodal tDCS, but significant effect of NIBS techniques (considering all studies that used low frequency rTMS or cathodal tDCS over the non-lesioned hemisphere) in combination with SLT. No adverse events
Shah-Basak et al., 2016 [77] (exploring also rTMS effect)	140 patients, 8 studies (58 chronic patients, 45 subacute, 37 mixed)	Anodal, cathodal	Naming accuracy	Chronic patients: SMD = 0.320, 95% CI: 0.17–0.47 Subacute patients: SMD = 0.283, 95% CI: −0.27–0.83 All patients: SMD = 0.395, 95% CI: 0.28–0.51	Evidence of the effectiveness of tDCS in combination with SLT in chronic but not in subacute patients while TMS in combination with SLT was significantly efficient in both chronic and subacute populations
Rosso et al., 2018 [78]	68 chronic patients, 7 studies	Anodal, cathodal	Naming accuracy	SMD = 0.802, 95% CI: 0.273–1.333	Significant dose-dependent effect. Difference between active and sham stimulations was higher in anodal versus cathodal conditions, higher after left versus right stimulation

SLT: speech language therapy; rTMS: repetitive transcranial magnetic stimulation; SMD: standardized mean difference; 95% CI: 95% confidence interval.

Table 4
Details of tDCS procedure for randomised clinical trials.

Study	Device/electrodes	Active procedure/current	Sham procedure	Details of electrodes location
Anodal targeting the left hemisphere				
Baker et al., 2010 [27]	Phoresor® II PM850; Iomed® Inc./saline-soaked sponge electrodes (5 × 5 cm)	Fade in: unknown Fade out: unknown Duration: 20 min Current density: 40 μA/cm²	Turned off after 30 s of stimulation	Active: anode placed targeting the voxels with the highest Z-scores associated with correct naming/location based on MNI coordinates, and anatomical locations were determined using the Talairach Daemon Reference: cathode electrode placed on the right shoulder
Fiori et al., 2011 [28]	Eldith® (neuroConn® GmbH)/ surface-soaked sponge electrodes (5 × 7 cm)	Fade in: unknown Fade out: unknown Duration: 20 min Current density: 28.6 μA/cm²	Not described	Active: anode over CP5 of the extended International 10–20 System for EEG electrode placement. y-z MNI coordinates of the vertices of the rectangle electrode were: I = −27, 40; II = −79, 34; III = −66–8; and IV = −20, −7. Based on the reconstructed delimitation of the tCDS and CP5 areas, CP5 was positioned in the posterior part of the superior temporal gyrus (Wernicke's area) and the tDCS area together with the posterior part of the superior temporal gyrus, included the posterior portion of the middle temporal gyrus, the inferior part of the supramarginal and angular gyri, and part of the middle and inferior occipital gyri Reference: cathode placed over contralateral fronto-polar cortex
Fridriksson et al., 2011 [29]	Phoresor® II PM850; Iomed® Inc./saline-soaked sponge electrodes (5 × 5 cm)	Fade in: unknown Fade out: unknown Duration: 20 min Current density: 40 μA/cm²	Turned off after 30 s of stimulation	Active: anode placed targeting the voxels with the highest Z-scores associated with correct naming/location based on MNI coordinates, and anatomical locations were determined using the Talairach Daemon Reference: cathode electrode placed on the right forehead
Marangolo et al., 2011 [30]	Eldith® (neuroConn® GmbH)/ surface-soaked sponge electrodes (5 × 7 cm)	fade in: unknown fade out: unknown duration: 20 min current density: 28.6 μA/cm²	Turned off after 30 s of stimulation	Active: anode placed over BA 44/45, position defined according to 10–20 System for EEG electrode placement; using the Munster T2T-converter to determine the position on the EEG system Reference: cathode positioned over the contra lateral supraorbital region
Marangolo et al., 2013 [31]	Eldith® (neuroConn® GmbH)/ surface-soaked sponge electrodes (5 × 7 cm)	Fade in: unknown Fade out: unknown Duration: 20 min Current density: 28.6 μA/cm²	Turned off after 30 s of stimulation	Active: anode over F5 (Broca's area) or CP5 (Wernike's area) of the extended International 10–20 System for EEG electrode placement (see above Fiori et al., 2011[28]) Reference: cathode placed over contralateral fronto-polar cortex
Volpato et al., 2013 [32]	Eldith® (neuroConn® GmbH)/ surface-soaked sponge electrodes (5 × 7 cm)	Fade in: unknown Fade out: unknown Duration: 20 min Current density: 57.1 μA/cm²	Turned off after 30 s of stimulation	Active: anode over the crossing point between T3-Fz and F7-Cz according to the extended International 10–20 System for EEG electrode placement Reference: cathode placed over contralateral supraorbital area
Marangolo et al., 2013 [33]	Eldith® (neuroConn® GmbH)/ surface-soaked sponge electrodes (5 × 7 cm)	Fade in: unknown Fade out: unknown Duration: 20 min Current density: 28.6 μA/cm²	Turned off after 30 s of stimulation	Active: anode over F5 (Broca's area) or CP5 (Wernike's area) of the extended International 10–20 System for EEG electrode placement (see above Fiori et al., 2011[28]) Reference: cathode placed over contralateral fronto-polar cortex
Polanowska et al., 2013 [34]	Channel DC-Stimulator Plus NeuroConn/surface saline-soaked 5 × 7 cm	Fade in: unknown Fade out: unknown Duration: 10 min Current density: 28.6 μA/cm²	1 mA for first 25 s of 10-min stimulation period	Active: anode over the crossing point between T3-Fz and F7-Cz according to the extended International 10–20 System for EEG electrode placement Reference: cathode placed over contralateral supraorbital area
Polanowska et al., 2013 [35]	Channel DC-Stimulator Plus NeuroConn/surface saline-soaked 5 × 7 cm	Fade in: unknown Fade out: unknown Duration: 10 min Current density: 28.6 μA/cm²	1 mA for first 25 s of 10-min stimulation period	Active: anode over the crossing point between T3-Fz and F7-Cz according to the extended International 10–20 System for EEG electrode placement Reference: cathode placed over contralateral supraorbital area
Marangolo et al., 2014 [36]	Eldith® (neuroConn® GmbH)/ surface-soaked sponge electrodes (5 × 7 cm)	Fade in: unknown Fade out: unknown Duration: 20 min Current density: 28.6 μA/cm²	Turned off following 30 s of stimulation	Active: anode over F5 (Broca's area) or CP5 (Wernike's area) of the extended International 10–20 System for EEG electrode placement Reference: cathode placed over contralateral fronto-polar cortex

Table 4 (*Continued*)

Study	Device/electrodes	Active procedure/current	Sham procedure	Details of electrodes location
Vestito et al., 2014 [37]	HDCstim (Newronika)/plant cellulose sponge electrodes (5×5 cm) + electroconductive gel	Fade in: unknown Fade out: unknown Duration: 20 min Current density: 60 μA/cm^2 Impedance was kept consistently < 5 kΩ	Turned off 30 s after the beginning of the stimulation and turned on for the last 30 s	Active: anode over the crossing point between T3-Fz and F7-Cz according to the extended International 10–20 System for EEG electrode placement Reference: cathode placed over contralateral supraorbital area
Campana et al., 2015 [38]	Eldith® (neuroConn® GmbH)/surface-soaked sponge electrodes (5×7 cm)	Fade in: unknown Fade out: unknown Duration: 20 min Current density: 57.1 μA/cm^2	Ramped up to 2 mA and slowly decreased over 30 s	Active: anode over F5 of the extended International 10–20 System for EEG electrode placement Reference: cathode placed over contralateral supraorbital area
Wu et al., 2015 [39]	IS200, Chengdu/saline-soaked sponge electrodes (4.5×5.5 cm)	Fade in: unknown Fade out: unknown Duration: 20 min Current density: 48.5 μA/cm^2	Turned off after 30 s of stimulation	Active: anode over the crossing point between T3-P3 and C3-T5 according to the extended International 10–20 System for EEG electrode placement Reference: cathode placed on the unaffected shoulder
Meinzer et al., 2016 [40]	DC-Stimulator Plus (NeuroConn)/surface-soaked sponge electrodes anode (5×7 cm) cathode (10×10 cm)	Fade in: 10 s Fade out: 10 s Duration: 20 min Current density: 28.6 μA/cm^2	Ramping up and at 1 mA only for 30 s before ramping down	Active: anode over C3 of the extended International 10–20 System for EEG electrode placement Reference: cathode placed over contralateral supraorbital area
Branscheidt et al., 2017 [41]	DC-Stimulator Eldith® (neuroConn® GmbH)/surface-soaked sponge electrodes: anode (5×5 cm) cathode (5×7 cm)	Fade in: 10 s Fade out: 10 s Duration: 20 min Current density: 80 μA/cm^2	Ramping up and at 2 mA only for 30 s before ramping down	Active: anode over the hot spot of the cortical hand area in the left primary Motor cortex found using TMS Reference: cathode placed over contralateral supraorbital area
Santos et al., 2017 [42]	Device/non-described/saline-soaked sponge electrodes. anode (10×10 cm) cathode (5×7 cm)	Fade in: unknown Fade out: unknown Duration: 20 min Current density: 20 μA/cm^2 Estimated current density taking into account electrical properties of the tissues: from 0–0.522 V/m	Turned off after 20 s of stimulation	Active: anode placed over the Broca's area (no more description) Reference: cathode centred horizontally over the F8 of the extended International 10–20 System for EEG electrode placement
Spielmann et al., 2018a [43]	DC-Stimulator Eldith® (neuroConn® GmbH)/surface-soaked sponge electrodes (5×7 cm)	Fade in: 15 s Fade out: 15 s Duration: 20 min Current density: 28.6 μA/cm^2	Fade in: 15 s Duration 30 s Fade out: 15 s	Active: anode over F5 of the extended International 10–20 System for EEG electrode placement Reference: cathode over FP2 (over contralateral supraorbital area)
Spielmann et al., 2018b [44]	DC-Stimulator Eldith® (neuroConn® GmbH)/surface-soaked sponge electrodes (5×7 cm)	Fade in: 15 s Fade out: 15 s Duration: 20 min Current density: 28.6 μA/cm^2	Fade in: 15 s Duration 30 s Fade out: 15 s	Active: anode over F5 of the extended International 10–20 System for EEG electrode placement (LIFG) or over CP5 (LSTG) Reference: cathode over FP2 (over contralateral supraorbital area)
Woodhead et al., 2018 [45]	DC-Stimulator® (neuroConn® GmbH)/surface-soaked sponge electrodes (5×7 cm)	Fade in: 15 s Fade out: 15 s Duration: 20 min Current density: 57.1 μA/cm^2	Fade in: 15 s Duration 30 s Fade out: 15 s	Active: anode over FC5 of the extended International 10–20 System for EEG electrode placement Reference: cathode over contralateral supraorbital area
Fridriksson et al., 2018 [46]	Phoresor® II PM850; Iomed® Inc./saline-soaked sponge electrodes (5×5 cm)	Fade in: unknown Fade out: unknown Duration: 20 min Current density: 40 μA/cm^2	Gradually decreased over 15 s after 30 s of stimulation	Active: anode placed targeting the voxels with the highest Z-scores associated with correct naming/location based on MNI coordinates, and anatomical locations were determined using the Talairach Daemon Reference: cathode placed over contralateral supraorbital area

Table 4 (*Continued*)

Study	Device/electrodes	Active procedure/current	Sham procedure	Details of electrodes location
Pestalozzi et al., 2018 [49]	DC-Stimulator plus® (neuroConn® GmbH)/saline-soaked sponge electrodes (anode (5 × 5 cm) cathode (5 × 7 cm)	Fade in: 30s Fade out: 15 s Duration: 20 min Current density: 40 μA/cm²	Fade in: 30 s Duration 40 s Fade out: 15 s	Active: anode over F3 of the extended International 10–20 System for EEG electrode placement individually located with the Beam F3 system [79] Reference: cathode over contralateral supraorbital area
Other target and/or polarity				
Monti et al., 2008 [50]	DC-Stimulator Eldith® (neuroConn® GmbH)/surface-soaked sponge electrodes (5 × 7 cm)	Fade in: unknown Fade out: unknown Duration: 20 min Current density: 57.1 μA/cm²	Turned off following 10 s of stimulation	Active: anode or cathode over the crossing point between T3-Fz and F7-Cz (Broca's area) according to the extended International 10–20 System for EEG electrode placement or 2 cm over the ion (occipital stimulation) Reference: anode or cathode above the right shoulder
Kang et al., 2011 [51]	Phoresor® II PM850; Iomed® Inc./saline-soaked sponge electrodes (5 × 5 cm)	Fade in: unknown Fade out: unknown Duration: 20 min Current density: 80 μA/cm²	Turned off following 1 min of stimulation	Active: cathode over F8 of the extended International 10–20 System for EEG electrode placement Reference: anode over contralateral supraorbital area
Floel et al., 2011 [52]	Schneider Electronic, Gleichen/surface-soaked sponge electrodes (active 5 × 7 cm and reference 10 × 10 cm)	Fade in: few seconds (non-detailed) Fade out: unknown Duration: 20 min Current density: 28.6 μA/cm²	Turned off following 30s of stimulation	Active: anode or cathode centered on Talairach coordinates 57/-30/3 using the Münster T2T-converter to determine position on the scalp; http://wwwneuro03.uni-muenster.de/ger/t2tconv/ Reference: anode or cathode over contralateral supraorbital area
You et al., 2011 [53]	Phoresor® II PM850; Iomed® Inc./saline-soaked sponge electrodes (5 × 7 cm)	Fade in: unknown Fade out: unknown Duration: 30 min Current density: 57.1 μA/cm²	Fade in: 30s Duration 0s Fade out: 30s	Active: anode CP5 (Wernike's area) or cathode over CP6 of the extended International 10–20 System for EEG electrode placement Reference: anode or cathode over contralateral supraorbital area
Vines et al., 2011 [54]	Phoresor®; Iomed® Inc./saline-soaked sponge electrodes (anode = 16.3 cm² cathode = 30 cm²)	Fade in: few seconds (non-detailed) Fade out: unknown Duration: 20 min Current density: 73.6 μA/cm²	Fade in: 30s Duration 0s Fade out: 0s	Active: anode over the RIFG, centered approximately 2.5 cm posterior to F8 of the 10–20 International EEG system for electrode placement Reference: cathode over contralateral supraorbital area
Marangolo et al., 2013 [55]	Eldith® (neuroConn® GmbH)/surface-soaked sponge electrodes (5 × 7 cm)	Fade in: unknown Fade out: unknown Duration: 20 min Current density: 56.1 μA/cm²	Current was ramped up to 2 mA and slowly decreased over 30s	Anode placed over the ipsilesional and the cathode over the contralesional inferior frontal gyrus (IFG) F5 and F6 of the extended International 10–20 system for EEG electrode placement
Lee et al., 2013 [56]	Phoresor® II PM850; Iomed® Inc./saline-soaked sponge electrodes (5 × 5 cm)	Fade in: unknown Fade out: unknown Duration: 30 min Current density: 80 μA/cm²	No sham left anodal VS bilateral stimulation	Active: anode F7 or cathode over F8 of the extended International 10–20 System for EEG electrode placement Reference: anode or cathode appliednto the buccinator muscle of the same side
Marangolo et al., 2014 [57]	Eldith® (neuroConn® GmbH)/surface-soaked sponge electrodes (5 × 7 cm)	Fade in: unknown Fade out: unknown Duration: 20 min Current density: 56.1 μA/cm²	Current was ramped up to 2 mA and slowly decreased over 30 s	Anode placed over the ipsilesional and the cathode over the contralesional inferior frontal gyrus (IFG) F5 and F6 of the extended International 10–20 system for EEG electrode placement
Cipollari et al., 2015 [58]	Eldith® (neuroConn® GmbH)/surface-soaked sponge electrodes (5 × 7 cm)	Fade in: unknown Fade out: unknown Duration: 20 min Current density: 56.1 μA/cm²	Current was ramped up to 2 mA and slowly decreased over 30 s	Active: anode over F8 of the extended International 10–20 System for EEG electrode placement Reference: cathode over contralateral frontopolar cortex
Shah-Basak et al., 2015 [59]	Eldith 1 Channel DC-Stimulator Plus (Magstim)/surface-soaked sponge electrodes (5 × 5 cm)	Fade in: 30 s Fade out: 30 s Duration: 20 min Current density: 80 μA/cm²	Fade in: 30 s Duration 0 s Fade out: 30 s	Active: anode or cathode over F3 and anode or cathode over F4 of the extended International 10–20 System for EEG electrode placement Reference: placed over the contralateral mastoid.

Table 4 (*Continued*)

Study	Device/electrodes	Active procedure/current	Sham procedure	Details of electrodes location
de Aguiar et al., 2015 [60]	Eldith® (neuroConn® GmbH)/ surface-soaked sponge electrodes (5 × 7 cm)	Fade in: 5 s Fade out: unknown Duration: 20 min Current density: 28.6 μA/ cm^2	Fade in: 5 s Duration 30 s Fade out: unknown And same stimulation 20 min later	Anode over left perilesional areas defined using individual MRI. Placement over the defined perilesional areas used the extended International 10–20 System for EEG electrode placement and cathode over the homologous contralateral area
Marangolo et al., 2016 [61]	Eldith® (neuroConn® GmbH)/ surface-soaked sponge electrodes (5 × 7 cm)	Fade in: unknown Fade out: unknown Duration: 20 min Current density: 56.1 μA/ cm^2	Not described	Anode placed over the ipsilesional and the cathode over the contralesional inferior frontal gyrus (IFG) F5 and F6 of the extended International 10–20 system for EEG electrode placement
Norise et al., 2017 [62]	Eldith 1 Channel DC-Stimulator Plus (Magstim)/surface-soaked sponge electrodes (5 × 5 cm)	Fade in: 30 s Fade out: 30 s Duration: 20 min Current density: 80 μA/ cm^2	Fade in: 30 s Duration 0 s Fade out: 30 s	Active: anode or cathode over F3 and anode or cathode over F4 of the extended International 10–20 System for EEG electrode placement Reference: placed over the contralateral mastoid
Marangolo et al., 2017 [63]	EMS (Bologna)/surface-soaked sponge electrodes (5 × 7 cm)	Fade in: unknown Fade out: unknown Duration: 20 min Current density: 56.1 μA/ cm^2	Turned off following 30 s of stimulation	Active: cathode placed 1 cm under and 4 cm lateral to the inion Reference: anode over the right shoulder on the deltoid muscle
Marangolo et al., 2017 [64]	Eldith 1 Channel DC-Stimulator Plus (Magstim)/surface-soaked sponge electrodes (5 × 7 cm)	Fade in: unknown Fade out: unknown Duration: 20 min Current density: 56.1 μA/ cm^2	Turned off following 30 s of stimulation	Active: anode or cathode placed on the 10th thoracic vertebra (spanned from the ninth to the 11th thoracic vertebrae) Reference: anode or cathode over the right shoulder on the deltoid muscle
Silva et al., 2018 [65] (double-blinded vs sham)	Neurodyn/not detailed	Fade in: unknown Fade out: unknown Duration: 20 min Current density: unknown	Fade in: 30 s Duration 0 s Fade out: 30 s	Active: cathode over F8 of the extended International 10–20 System for EEG electrode placement Reference: anode over contralateral supraorbital area

MNI: Montreal Neurological Institute; BDAE: Boston Diagnostic Aphasia Examination; fMRI: functional MRI; LIFG: left inferior frontal gyrus; LSTG: left superior temporal gyrus; DLPFC: dorsolateral prefrontal cortex; MIT: melodic intonation therapy; RIFG: right inferior frontal gyrus; SLT: speech language therapy; TMS: transcranial magnetic stimulation; WAB AQ: Western Aphasia Battery Aphasia Quotient.

Table 5
Details of tDCS procedure for other studies or case reports.

Study (design)	Device/electrodes	Details of active procedure/details of current	Sham procedure	Details of electrodes location
Jung et al., 2011 [67]	Phoresor® II PM850; Iomed® Inc./ saline-soaked sponge electrodes (35 cm^2)	Fade in: 10 Fade out: unknown Duration: 20 min Current density: 28.6 $\mu A/cm^2$	No sham	Active: cathode over Broadmann area 45 defined as the space between T4-Fz and F8-Cz of the extended International 10–20 System for EEG electrode placement Reference: anode over contralateral forehead
Cherney et al., 2013 [68]	Dupel Iontophoresis System, Empi./ cathode saline-soaked sponge electrodes (8 cm^2) anode self-adhesive carbonized (48 cm^2)	Fade in: unknown Fade out: unknown Duration: 13 min Current density: 125 $\mu A/cm^2$ Charge density: 96 mC/cm^2	No sham	Determination of cathode placement using fMRI and the neuronavigation system Reference: anode over contralateral forehead
Santos et al., 2013 [69]	Device non-described/saline-soaked sponge electrodes (35 cm^2)	Fade in: unknown Fade out: unknown Duration: 20 min Current density: 56.1 $\mu A/cm^2$	No sham	Active: cathode over the C4 of the extended International 10–20 System for EEG electrode placement Reference: anode over contralateral forehead
Galletta et al., 2015 [70] (crossover, double-blinded vs sham)	Soterix Medical 1 × 1/saline-soaked sponge electrodes (35 cm^2)	Fade in: 60 s Fade out: unknown Duration: 20 min Current density: 28.6 $\mu A/cm^2$	Fade in: 60 s Duration 0 s Fade out: 60 s	Active: anode over F7 of the extended International 10–20 System for EEG electrode placement Reference: cathode over contralateral supraorbital area
Manenti et al., 2015 [71]	Unknown	Fade in: unknown Fade out: unknown Duration: 25 min Current density: unknown	No sham	Anode over the left DLPFC and cathode over the right DLPFC. No more details
Sebastian et al., 2017 [72] (crossover, double-blinded vs sham)	ActivaDose II stimulator (ActiveTec Inc.)/saline-soaked sponge electrodes (25 cm^2)	Fade in: unknown Fade out: unknown Duration: 20 min Current density: 80 $\mu A/cm^2$	Turned off following 30 s of stimulation	Active: cathode placed 1 cm under and 4 cm lateral to the inion Reference: anode over the right shoulder on the deltoid muscle supraorbital area
Sandars et al., 2018 [73] (case report)	DC-Stimulator plus® (neuroConn® GmbH)/saline-soaked sponge electrodes (5 × 7 cm)	Fade in: 30 s Fade out: 30 s Duration: 20 min Current density: 80 $\mu A/cm^2$	Fade in: unknown Duration 60 s Fade out: 30 s	Active: anode or cathode over F5 and anode or cathode over FC6 of the extended International 10–20 System for EEG electrode placement Reference: placed over the contralateral shoulder

DLPFC: dorsolateral prefrontal cortex; fMRI: functional MRI.

improved verb generation [63]. Finally, stimulation of the spinal cord, involved in motor activity, had positive effects on verb naming [64].

3.4. Targeting the location of electrodes

Four studies used MRI to accurately locate the lesion and to place electrodes for each patient [27,46,60,68], targeting the voxels with the highest Z-scores associated with correct naming/location based on MNI coordinates for the 3 randomised clinical trials [27,46,60]. Another study first tried to find the "hot spot" of the left primary motor cortex by using TMS to precisely stimulate this area with anodal tDCS [41]. Most of the studies used the international 10-20 electroencephalography (EEG) electrode positioning system to place active electrodes, and the return/reference electrode was placed over the contralateral fronto-polar cortex. Tables 4 and 5 summarise these locations and tDCS procedures. Fig. 3 shows the locations and polarity of studies that found significant effects of tDCS.

3.5. Stimulation parameters

The stimulation duration varied from 10 to 30 min, generally 20 min in most studies. In terms of intensity of the direct current, 19 studies used 2 mA, 16 studies 1 mA, 2 studies 1.2 mA and 1 study 1.5 mA. The estimated current density was 28.6 $\mu A/cm^2$ in most cases (range 20–80 $\mu A/cm^2$ because of the heterogeneity of devices and electrodes used). Tables 4 and 5 summarise details of the tDCS procedure and the hypothetical current maxima at the target location for studies that detailed it. The number of sessions also varied: from 1 session to 30 repeated sessions, but most studies proposed repeated sessions (5 or 10). This approach using repeated sessions seemed to confer a better effect of tDCS, suggesting a dose-dependent effect, as alluded in the most recent meta-analysis [78]. Another stimulation parameter that varied among studies was the combination of tDCS and language tasks (i.e., on-line versus off-line stimulation, without the language task). Six studies proposed off-line tDCS and only one found positive results versus sham stimulation [71].

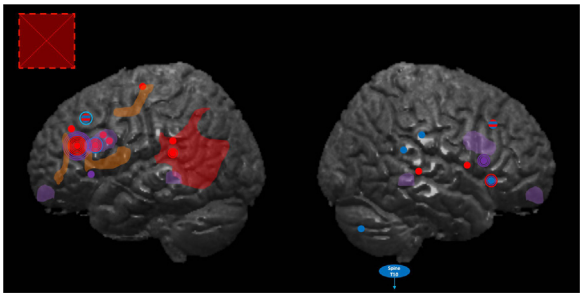

Fig. 3. Projections of the centre of the active electrodes over the cortex for randomised clinical trials that found significant results for tDCS. Each dot/circle represents one study that did not use individualised targets. Red: anode, blue: cathode, purple: bihemispheric (cathode over the right hemisphere and anode over the left one) for studies that used the 10/20 System for electroencephalography electrode placement based on MNI coordinates from Rojas et al., 2018 [80]. Striped dots correspond to effective anodal or cathodal stimulation based on individual response to treatment of patients from the same study. Red or orange colours correspond to areas targeted for anodal stimulation in studies based on individualised functional MRI (fMRI) results for tDCS, and purple colour corresponds to bihemispheric stimulation (cathode over the right hemisphere and anode over the left one) for 3 of the 4 studies that used fMRI for placement of electrodes. The red square represents the approximate size of electrodes used (25 cm^2). This figure allows for understanding variability between studies even if most of targeted areas are known to be crucially involved in language (Broca's area, Wernicke's area, motor cortex) or homologous ones. Opposite stimulation (i.e., anodal or cathodal) over the same area or over close areas even though under the active electrode significantly improved language tasks. This figure underlines the many challenges in better understanding the effects of tDCS on the brain and language networks.

3.6. Subacute vs chronic phase

In most studies, patients were in the chronic disease phase, more than 3 or 6 months after stroke. Only 5 studies explored the effects of tDCS in a subacute phase. Regarding language comprehension, tDCS over Wernicke's area improved auditory verbal comprehension in patients in the subacute phase (16 to 38 days after stroke) particularly using inhibition of the homologous right Wernicke's area, [53]. However, in the acute or subacute phase, tDCS did not seem to be effective in language production, and no significant differences were found between anodal tDCS versus LIFG and sham-tDCS [34,35]. These results were confirmed in a recent study including a large sample of patients: in the subacute phase (3 weeks to 3 months post-stroke), anodal tDCS effects did not differ from LIFG and sham-tDCS effects in the Boston Naming Test [43].

3.7. Outcome measures

In most studies, the outcome was an assessment of language performance such as naming tasks, fluency, reading or auditory verbal comprehension. Only one study explored the effect of tDCS on everyday communication [81].

3.8. Short- versus long-term effects

Several studies focused on very short-term effects of tDCS (i.e., outcomes were measured immediately after the stimulation). tDCS improved the accuracy of picture naming at 1 min after stimulation [50] and improved naming accuracy at 1 hr after stimulation [51]. Other studies have looked at medium-term effects (i.e., outcomes were measured 1, 2 or 3 weeks after the last stimulation). One week after the stimulation, improvements were noted in naming accuracy [27,46]; articulation accuracy and speed [55]; picture description, noun and verb naming [57]; speech fluency [58]; and verb generation [63] and verb naming [64]. Improvement in naming accuracy was also noted 2 weeks after the stimulation [52]. Improvement in naming accuracy and shorter naming latencies were noted 3 weeks after the stimulation [28] as was a reduction in reaction time naming of trained items [29]. Finally, other studies have looked at the long-term effects of tDCS (i.e., several months after stimulation). These studies showed improvements in naming performance 16 weeks after stimulation [37]; naming ability for trained and untrained items and generalisation to everyday communication 6 months after stimulation [40]; verb naming for treated and untreated verbs 48 weeks after stimulation [71]; or reading ability 3 months after stimulation [45]. However, some studies did not show a significant long-term effect of tDCS at 3 months after stimulation [34,35] or 6 months after stimulation [43,47]. Note that 3 of these studies [34,35,43] involved patients in the post-acute or subacute phase (see Table 1 for more details). Hence, tDCS might allow for beneficial long-term effects, except in the earliest phase after stroke.

4. Discussion

As shown in this systematic review, repeated sessions of tDCS combined with SLT enhanced rehabilitation in chronic post-stroke aphasia and thus provide an efficient tool to boost aphasia rehabilitation. However, some questions remain, and we discuss some challenges to better understand the mechanisms and the best use of this tool.

4.1. Brain targets, polarity and influence of the lesion

This review underlines the heterogeneity of the procedures used in the described studies. Most of these studies used a montage that permitted neuromodulation based on neural processes and known mechanisms, targeting areas involved in language processes or known to be involved in aphasia recovery and neuroplasticity. Indeed, because perilesional areas are known to be involved in aphasia recovery [82] as well as the spared left hemisphere (for review, see Hartwigsen and Saur, 2017 [12]), many studies explored the effects of facilitation of the left-damaged hemisphere, particularly targeting Broca's or Wernicke's area. However, only a few studies precisely targeted individualised perilesional crucial areas using an fMRI localiser based on the activity during language tasks before anodal tDCS. This approach takes into account the various sizes and/or location of lesions and thus the individual reorganisation of language networks but is expensive, time-consuming and not relevant for all patients in routine clinical practice. Moreover, fMRI maximal activation does not necessarily reflect crucial individual networks and neural processes [83], which should be enhanced to improve impaired language processes.

Another approach, much more possible in routine, is to place electrodes targeting a non-relevant individualised area by using the 10–20 System for EEG electrode placement combined with normalised imaging. However, this approach does not take into account the anatomical and functional changes due to the lesion or the perturbation of the stimulating currents during neuromodulation consecutive to the altered electrical tissue properties [84], which evolves over time. Indeed, altered electrical tissue properties are also modified over time after a stroke (subacute vs chronic phase) [85].

To optimise the effects of tDCS on impaired networks and to choose the relevant targeted area and polarity, we need a better understanding of the brain reorganisation, the time course of this reorganisation and the involvement of perilesional and contralesional cortices, in addition to the precise molecular mechanisms associated with non-invasive brain stimulation. Indeed, improvement was found after both anodal or cathodal stimulation over the right hemisphere, which could be considered counterintuitive in models of inter-hemispheric competition [15]. Inhibiting the right hemisphere might be useful only when its activity is too high and maladaptive but might be harmful when the right hemisphere activity is compensatory. Hence, bilateral modulation (anodal over the left and cathodal over the right relevant areas) might not necessarily be more efficient on aphasia, even if the 3 randomised trials described in this review found significant results. Only one study compared mono- or bihemispheric stimulation and the results were limited [56]. However, a recent study found that bihemispheric stimulation may be more effective in improving language learning in healthy older people [86]. This finding suggests the need for further research.

Moreover, the right hemisphere, particularly the right Broca-homolog and supplementary motor area, seems involved in the subacute phase of stroke, and language reorganisation needs these divergent processes before a normalisation and re-shifting of cortex activity toward the left at the chronic stage [87]. Hence, modulation of the same areas could have different effects depending on the post-stroke phase, which could explain the non-significant results of the recent study that aimed to facilitate the LIFG at the subacute phase [43]. Facilitation over the right hemisphere might have been more relevant in the subacute phase, considering the study of Saur et al. [88]. At a chronic stage, the role of the right cortex might be more complex than presented in models of inter-hemispheric competition. Some close areas in the right hemisphere seem associated with better or poorer recovery. Recent findings found that cortical hypertrophy in the temporal regions was associated with improving (right anterior middle temporal gyrus) or worsening (more posterior right middle temporal gyrus) behaviour, whereas hypertrophy in the precentral gyrus was associated with worsening behaviour in aphasic patients [89]. Hence, inhibiting the right frontal areas might enhance language and facilitating the right temporal region might modulate areas associated with both improvement and worsening, particularly with large electrodes (5×5 or 5×7 cm). This problem might have been avoided with high-definition tDCS — which should allow for precisely targeting some areas based on anatomical or functional imaging [90] — or rTMS.

Modulation of several areas that might have been considered less relevant for language processes improved aphasia. Hence, significant improvement was found after facilitation of the left primary motor cortex [81]. These results agree with recent studies that suggested the crucial need for motor networks for aphasia recovery [11,91]. Right cerebellum modulation also allowed for improvement [63], which shows the contribution of this structure in higher-level cerebral functions. Indeed, an abnormal response from the right cerebellum has been shown in aphasia, because of the absence of input from the damaged left frontal regions [92]. Finally, spinal modulation allowed for improvement [64]. This finding is surprising and might have been explained by the influence on activity along the ascending somatosensory pathways, affecting specific language networks associated with motor schemata.

4.2. tDCS procedure: devices, montage, current intensity

rTMS stimulation is based on an individualised approach calculating the rest motor threshold to determine the best intensity of stimulation taking into account variability of anatomical structures between the scalp and brain and inducing an effective magnetic field; tDCS does not permit such an approach. In most cases, the current density varied from 28 to 80 $\mu A/cm^2$ and impedance or the hypothetical current maxima at the target location is rarely described, so individual neural effects might differ with the same stimulation parameters. Indeed, the field distribution can be inhomogeneous, inducing possible variability between the hypothetical targeted area and the true stimulated area. Field distribution depends on several anatomical factors such as the thickness and composition of the overlying skull, the thickness of the cerebrospinal fluid layer between the cortex and skull and the sulcal depth. In addition, the field strength on the cortex or underneath an electrode is affected by the distance to the electrode edges and the distance to the return electrode [93].

Devices, current intensity and/or montage might affect the active and sham condition. Indeed, higher stimulation intensities might interfere with double-blinding. The current intensity of 2 mA induces skin redness that might interfere with assessor judgement, and participants seem to guess with accuracy whether they had received real or sham stimulation [94]. Future studies using tDCS should report detailed tDCS procedures and guarantees of successful blinding, such as questioning the patient after the end of the treatment or keeping a record of the reported sensations to control the double-blinding design.

Duration and frequency of tDCS should be taken into account. Most studies used a stimulation duration of 20 min, but tDCS lasted 10 or 30 min in several studies. This issue needs to be clarified, and the neural effects of tDCS need better understanding. Contrary to TMS, tDCS allows for a continuous stimulation that can engage neurophysiological homeostasis mechanisms. Indeed, neurons could adjust their activity, and this type of mechanism might produce a not-expected effect in terms of excitatory or inhibitory responses [95]. Moreover, the frequency and interval of repeated stimulations might contribute to different neural effects at a

molecular level in terms of the motor cortex [96]. Considering repeated sessions of tDCS combined with SLT, the frequency and interval between these sessions might also induce such variability and needs to be explored even if the most recent meta-analysis found a significant dose-dependent effect [78].

4.3. Factors not related to the tDCS procedure that influence effects

Behavioural treatment and tasks during tDCS might boost neuroplastic mechanisms. Off-line tDCS did not confer significant results in most of studies reviewed. Indeed, tDCS seems to induce an increased secretion of brain-derived neurotrophic factor (BDNF) and might mediate long-term potentiation via the N-methyl-D-aspartate system [97]. These mechanisms and neural growth factors facilitate recovery after stroke [98] and tDCS allows for increasing rehabilitation or training procedures optimising the state of activation of neurons recruited. From these findings, selecting the correct combination between the behavioural task and stimulation site is crucial to optimise the combined effects of tDCS and SLT. Hence, tDCS should target areas involved in the task in order to permit the best synaptic activation. For example, MIT, known to recruit right-brain areas, seems to be improved by anodal facilitation targeting the RIFG [54,58], whereas stimulation of the same target using opposite polarity boosts the effects of world retrieval training [51]. This finding underlines the rationale for a better understanding of neural processes of the various aphasia therapies.

Patients' characteristics also need to be considered for future studies, to select responding patients and propose neuromodulation. Genetic factors such as the BDNF genotype might interfere with the tDCS effects, and recent findings showed that patients with a typical BDNF genotype seemed to have milder symptoms and better improvement induced by anodal tDCS [48]. Other predictors of good response to treatment not related to the lesion should be explored.

4.4. Outcome measures

An assessment of language performances such as naming tasks was selected as an outcome in many studies reviewed and allows for better understanding the specific-language network reorganisation, but only one study explored the effects of tDCS on everyday communication [81]. However, based on the International Classification of Functioning, Disability and Health, an improvement of some deficiencies such as naming impairment is not always followed by an improvement of quality of life or less participation restrictions, whereas aphasia negatively affects functional outcome, mood, quality of life, participation and the ability to return to work [3–5]. In a recent study, the severity of aphasia appears to be strongly correlated with quality of life, even more than with cancer or Alzheimer disease [99]. A crucial challenge for future studies is to explore the impact of tDCS on communication and quality of life.

Further research is also needed to verify any long-term effects (beyond 1 month). Indeed, a recent large study did not find significant results at 24 weeks post-treatment [47]. Finally, long-term effects and outcome measures considering activity limitations, participation restrictions and quality of life need to be explored.

5. Conclusion

This systematic review summarises studies that explored the effects of tDCS on aphasia and highlights evidence of positive effects for chronic post-stroke patients despite some challenges that remain to be explored in future studies.

Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.rehab.2019.01.003.

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