HHS Public Access

Author manuscript

Clin Neurophysiol. Author manuscript; available in PMC 2017 February 25.

Published in final edited form as:

Clin Neurophysiol. 2016 January ; 127(1): 956–968. doi:10.1016/j.clinph.2015.04.069.

Effects of non-invasive brain stimulation on post-stroke dysphagia: A systematic review and meta-analysis of randomized controlled trials

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Abstract

Objective—The primary aim of this review is to evaluate the effects of non-invasive brain stimulation on post-stroke dysphagia.

Methods—Thirteen databases were systematically searched through July 2014. Studies had to meet pre-specified inclusion and exclusion criteria. Each study's methodological quality was examined. Effect sizes were calculated from extracted data and combined for an overall summary statistic.

Results—Eight randomized controlled trials were included. These trials revealed a significant, moderate pooled effect size (0.55; 95% CI = 0.17, 0.93; $p = 0.004$). Studies stimulating the affected hemisphere had a combined effect size of 0.46 (95% CI = −0.18, 1.11; $p = 0.16$); studies stimulating the unaffected hemisphere had a combined effect size of 0.65 (95% CI = 0.14, 1.16; $p = 0.01$). At long-term follow up, three studies demonstrated a large but non-significant pooled effect size (0.81, $p = 0.11$).

Conclusions—This review found evidence for the efficacy of non-invasive brain stimulation on post-stroke dysphagia. A significant effect size resulted when stimulating the unaffected rather than the affected hemisphere. This finding is in agreement with previous studies implicating the plasticity of cortical neurons in the unaffected hemisphere.

Significance—Non-invasive brain stimulation appears to assist cortical reorganization in post-stroke dysphagia but emerging factors highlight the need for more data.

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Conflict of interest: The authors declare no conflict of interest.

Appendix A. Supplementary data: Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clinph.2015.04.069.

Keywords

Transcranial magnetic stimulation (TMS); Transcranial direct current stimulation; (tDCS); Non-invasive brain stimulation; Unilateral lesion; Post-stroke population; Dysphagia

1. Introduction

Studies report that 50–81% of people who have a stroke experience swallowing problems (Hamdy, 2010; Meng et al., 2000). This impact is staggering when the cost implications and morbidity of post-stroke dysphagia are considered. Stroke patients with dysphagia cost more to treat (about $4,510 more per patient than a stroke patient without dysphagia) because their hospital stay is nearly doubled, they require more therapy, and they have more complications with worse outcomes (Bonilha et al., 2014; Altman et al., 2010). Further, mortality is significantly higher in stroke patients with dysphagia; they have a 2.6-fold increased rate of death (Sharma et al., 2001; Smithard et al., 1996).

1.1. The need for a novel approach

Considering these statistics, the lack of an effective and quick rehabilitation for post-stroke dysphagia is surprising. Relying on natural recovery is a slow and incomplete approach. Compensatory strategies, such as prescribing thickened liquids and tucking the chin, are likely to negatively impact the patient's quality of life or, with non-compliance, lead to a negative outcome. Further, exercise for dysphagia requires weeks of intensive training before sufficient strengthening occurs (Burkhead et al., 2007). A more efficient rehabilitation is needed.

Researchers have looked to non-invasive brain stimulation as a means to rehabilitate dysphagia, and various small studies have investigated whether non-invasive brain stimulation could be used as a treatment for post-stroke dysphagia. The state of the research is at the point where a synthesis of the extant literature would help to elucidate this treatment's overall effect.

The purpose of this systematic review and meta-analysis is to review non-invasive brain stimulation on post-stroke dysphagia by examining evidence produced by randomized controlled trials and synthesizing their results. The research question is: Are the effects of non-invasive brain stimulation on swallowing in post-stroke dysphagic patients positive, and what can be learned about the best use of these technologies to improve outcomes? Variables of interest include: hemispheric targets in swallowing innervation, duration of stimulation, stimulation modality, and long-term follow up.

1.2. Review of tDCS and TMS

Non-invasive brain stimulation is based on the principle of neu-roplasticity, best defined as changes in neuronal pathways to increase neural functioning via synaptogenesis, reorganization, and network strengthening and suppression. The two most commonly used techniques are tDCS and TMS.

1.2.1. Transcranial direct current stimulation (tDCS)—Transcranial direct current stimulation (tDCS) provides a steady flow of low-intensity, electrical current between a positive and negative electrode placed strategically to target an area of the cortex. Anodal tDCS increases the excitability of cortical neurons by shifting the polarity of their resting membrane potential, thereby increasing the chance of depolarization. It has short-term effects that are mediated through changes in membrane potentials via sodium and calcium channels and other processes like GABAergic inhibition (Stagg et al., 2009; Ardolino et al., 2005; Islam et al., 1995). It also has been shown to have longer lasting effects, which occur through N-methyl-D-aspartate (NMDA) receptors, seen in long term potentiation and long term depression, via neurotrophic factors such as brain-derived neurotrophic factor (BDNF) (Fritsch et al., 2010; Liebetanz et al., 2002).

The effects of the short-term and long-term mechanisms have been witnessed from one hour up to weeks after the stimulation (Brunoni et al., 2012; Priori, 2003). For these reasons, tDCS has a posited therapeutic application to post-stroke rehabilitation.

1.2.2. Transcranial magnetic stimulation (TMS)—Another technique is transcranial magnetic stimulation (TMS). Here, a copper wire coil is placed over the targeted area of the cortex. During TMS, a brief, high current pulse is produced in a coil of wire, which in turn produces a magnetic field with lines of flux traversing perpendicularly to the plane of the coil. At the right strength, it can cause depolarization of the targeted neurons. Repetitive TMS (rTMS) is simply the repeated application of TMS. Pulses at a low frequency (~1 Hz) have an inhibitory effect by slowing neuronal excitability. On the other hand, pulses at a high frequency (≥3 Hz) increase the excitability of the neurons.

Studies have demonstrated that the neurophysiological effects of TMS include short-term effects via voltage-gated channels and sodium and calcium flow velocity (Wagner et al., 2007; Theodore, 2003). Other studies have demonstrated its influence on neurotransmitters. TMS has demonstrated an increase in gluta-mate and a decrease in $GABA_A$ (Ridding and Rothwell, 2007; Michael et al., 2003; Zangen and Hyodo, 2002). As in tDCS, post-stimulatory effects of TMS lasting beyond the treatment session have been documented. Longer lasting effects are likely due to factors like increases in NMDA-receptor activation (Quartarone, 2013).

1.2.3. tDCS versus TMS—Both tDCS and TMS are relatively safe forms of non-invasive brain stimulation. The word ‘relatively’ is preferred because even though there is no reason to suspect harm from the low-intensity protocols, much is unknown about the limits of current density, repeated applications, and long-term safety. Common safety concerns include seizures, scalp irritation or burns, and a localized headache or discomfort. For more detailed discussions about safety concerns, the reader is referred to other publications (*tDCS*: Bikson et al., 2009; Nitsche et al., 2003; Priori, 2003; McCreery et al., 1990; Agnew and McCreery, 1987; *TMS*: Rossi et al., 2009; Machii et al., 2006; Wassermann, 1998).

No studies investigating motor improvement have documented drastically different outcomes between the two techniques (Takeuchi and Izumi, 2012). Both have the potential to be performed as sham stimulation, an important quality for clinical trials (although Fregni

and Pascual-Leone, 2007 suggest that TMS is more difficult to produce as an active sham). The two techniques can also be adjusted to upregulate, downregulate, and target different areas of the cortex.

However, there are several important differences between the techniques. First, and most clearly, TMS is magnetic stimulation resulting from rapidly changing magnetic fields, and tDCS is electric, driven by a battery-powered device. Second, TMS generates depolarization whereas tDCS only modifies the excitability threshold of targeted neurons. This can be seen by a level of current density nearly 30 times as intense (A/m^2) with TMS than with tDCS at the level of cortical grey matter (Wagner et al., 2007). Third, the wire coils for rTMS focus the magnetic field, compared to the wide electrodes used for tDCS. TDCS has been shown to provide a wider spread of current density magnitudes, suggesting that more tissue receives the stimulation with tDCS than with TMS (Wagner et al., 2007). It should be noted, however, that spread does still occur in rTMS. Fourth, models have shown that the skull shunts tDCS currents across the scalp's surface. TMS currents appear to reach their maximum current density slightly deeper at the level of the cerebral spinal fluid (Wagner et al., 2007). Lastly, TMS can be applied in a fraction of a second with one pulse whereas tDCS does not have this capability. Of particular interest to this review is how tDCS and TMS, looked at together and separately, influence dys-phagia in the post-stroke population.

1.3. Variables of interest in non-invasive brain stimulation

1.3.1. Hemispheric targets in swallowing innervation—Although swallowing is a bilaterally innervated process, strong evidence by multiple researchers suggests that there is lateralization to a dominant hemisphere (Lowell et al., 2012; Li et al., 2009; Malandraki et al., 2009; Hamdy et al., 1998a, 1997; Hamdy et al., 1996; Robbins et al., 1993; Barer, 1989; Robbins and Levine, 1988; Gordon et al., 1987). A lesion in the dominant hemisphere is likely to result in oropharyngeal dysphagia leaving intact, but weaker, projections from the non-dominant side (Teismann et al., 2011; Li et al., 2009; Khedr et al., 2008; Hamdy et al., 1998b, 1997b, 1996). Multiple studies have shown that re-organizing and increasing the strength of the contralesional hemispheric projections help to rehabilitate dysphagia (Park et al., 2013; Michou et al., 2012; Teismann et al., 2011; Fraser et al., 2002).

Stimulating the lesioned or unlesioned hemisphere remains a controversial topic, as evidence is mixed as to which method best optimizes the recovery of post-stroke dysphagia. That is, some studies have stimulated the lesioned hemisphere (Yang et al., 2012; Khedr et al., 2009). This is believed to either restore output from the lesioned side (as it does for corticospinal pathways Pomervoy et al., 2007) or counteract suppressive effects from the contralesional hemisphere. Other studies aim to inhibit the intact, contralesional projections that are believed to be hyperactive post-stroke (Yun et al., 2011; Verin and Leroi, 2009). The theory behind this approach is that there is increased transcallosal inhibition that occurs after stroke and decreasing it helps to recover the swallow. And yet other studies have stimulated the contralesional hemisphere as a means to encourage excitability and plasticity in what is believed to be the ‘weaker side’ (Vasant et al., 2014; Park et al., 2013; Kumar et al., 2011). Clearly, research is still investigating the mechanisms at play in lesioned or contralesional hemispheric stimulation.

1.3.2. Duration of stimulation—While published studies have not generally provided a rationale, it is likely that the choice of stimulation duration is made considering safety guidelines. In general, tDCS studies tend to apply stimulation for 5–30 min and rTMS for 5–20 min, although rTMS duration depends on the number of pulses and how many trains of pulses. It is unclear how this parameter contributes to rehabilitation. A review of anodal tDCS to the motor cortex in healthy and stroke participants suggested larger effects with 13 min of stimulation than 10 min (Bastani and Jaberzadeh, 2012). No studies could be found investigating the influence of rTMS duration per session on outcomes. However, studies have shown that the pattern of rTMS pulses can influence outcomes. In fact, long continuous theta bursts 40 seconds long have been shown to produce effects opposite of the excitatory results seen with 2-second intermittent bursts: longer trains of rTMS stimulation were more suppressive (Cantarero et al., 2013; Huang et al., 2005).

The rationale for duration in terms of the number of days of stimulation is even more unclear. Study protocols have ranged from 1 to 20 days in daily or twice daily sessions without any stated rationale (Wagner et al., 2007). On the whole, there is limited data to clarify the impact of stimulation duration on outcomes, in both time per session and number of days.

1.3.3. Stimulation modality—Another consideration of unknown influence is tDCS versus TMS. The question here is if there is a difference in outcomes depending on the stimulation type. Until now, no studies have attempted to answer this question despite a myriad of reviews comparing the two techniques. This may be because they are too different to be compared, namely in their stimulation type, strength, focal beam, and duration. TMS has parameters like frequency, intensity, and number of pulses that distinguish it from tDCS parameters such as the amplitude and stimulation duration (see Section 1.2.3). In these ways, the applications are not comparable. Yet this study suggests that a realistic question is which type of stimulation should be used? In 2012, a review of non-invasive brain stimulation on post-stroke motor recovery posed this question (Takeuchi and Izumi, 2012), as did a more recent review (Simonetta-Moreau, 2014). Neither article found an answer. This review will stratify the identified studies by stimulation type as a means to begin a discussion to address this question.

1.3.4. Long-term follow up—Several studies have investigated the lasting effects of non-invasive brain stimulation on post-stroke motor outcomes and have reported results in favor of the extended effects from 6 days to even 6 months after stimulation (Khedr et al., 2013; Hesse et al., 2011; DiLazzaro et al., 2010; Kim et al., 2009; Boggio et al., 2007). Caution must be taken before jumping to conclusions, however, because multiple syntheses of these data have yielded non-significant results, although they trend in a positive direction (Ludemann-Podubecka et al., 2014; Marquez et al., 2013; Bastani and Jaberzadeh, 2012).

To date, only a handful of studies have reported on long-term outcome measures specifically related to swallowing (Park et al., 2013; Shigematsu et al., 2013; Yang et al., 2012; Khedr et al., 2009). It has been suggested that “repeated sessions, with cumulative effect, seem to be superior to a single session, and are needed to induce a sustained effect” (Fregni and Pascual-Leone, 2007, p. 390). On the other hand, two reviews have noted that there is no

evidence to suggest that non-invasive brain stimulation is capable of long-lasting effects and, if it was, then it would be unethical to use it on healthy subjects (Doeltgen, 2014; Ridding and Rothwell, 2007). Non-invasive brain stimulation clearly has created more questions than answers due to its multifaceted variables as simple as type, duration, and long-term efficacy.

2. Methods

2.1. Search strategy

The lead author searched the following 13 electronic databases from their inception to July 2014: ASHA journals, CINHAL, Cochrane database of systematic reviews, Embase, PEDro, ProQuest, PSYCHInfo, PUBMED, RehabData, Science Direct, Scopus, TRIP, and Web of Science. Google Scholar, ClinicalTrials.gov, and www.controlled-trials.com were also searched. Additionally, literature was identified by citation tracking in reference lists from identified papers. A hand search of all relevant references and authors was also completed. In an effort to identify all eligible trials and grey literature, the author contacted researchers in the field to obtain the most current information regarding data and ongoing studies and searched relevant special interest groups for possible studies. The following keywords were used in combinations for database searches: *dysphagia, swallowing, deglutition, transcranial neurostimulation, cortical stimulation, brain, rehabilitation, swallow, transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and non-invasive brain stimulation*. See Appendix A for an example of a specific search term and subject headings.

2.2. Selection criteria

Two clinician reviewers, blinded from one another's results, included or excluded retrieved studies by screening titles and abstracts using pre-specified inclusion and exclusion criteria:

2.2.1. Inclusion criteria

1. The study used tDCS, TMS, or rTMS as an intervention for human adults with post-stroke dysphagia.
2. Study outcomes related to swallowing: swallowing physiology measurements, functional outcomes of swallowing, quality of life related to swallowing, diet scales, dysphagia symptom scales, or health outcomes related to swallowing.

2.2.2. Exclusion criteria

1. The subjects' pathology was something other than unilateral stroke (i.e., brainstem infarction).
2. The subjects had pre-existing muscular or neurologic disorders or pre-existing dysphagia (i.e., Parkinson's disease).
3. The participants were healthy (i.e., pathology was induced via a simulated lesion).
4. The article was not a randomized controlled trial.
5. The swallowing outcomes involved only esophageal measures.

6. The study received a PEDro scale rating of “poor,” defined as 3 or less, or the abstract reported 75% or less of the items on the ‘PRISMA for Abstracts Checklist.’

7. Not enough data was reported or able to be calculated after attempts to contact the corresponding author.

2.3. Process of identification

Ambiguous titles and abstracts were sent to full-text review so as not to erroneously exclude potential studies. All languages were included. Of note, studies were *not* excluded if the subjects received a combination of therapeutic interventions (i.e. concurrent non-invasive brain stimulation and another secondary intervention). This is because even though paired stimulation presents a confounding variable, researchers are in a state of clinical equipoise about treating patients with transcranial neurostimulation alone and are ethically obligated to provide some other form of treatment to enrolled subjects. Further, non-invasive brain stimulation is rarely used alone and inclusion of paired stimuli increases the sample size and allows for greater generalization.

Fig. 1 displays the flow chart of studies in the PRISMA format (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

2.4. Quality assessment

Two reviewers read each of the final included full-text articles and independently assigned a quality marker to each using the validated Physiotherapy Evidence Database (PEDro) scale (Moseley et al., 2002; Maher et al., 2003). The maximum score on this scale is 10. A final score of 9 to 10 is considered excellent, 6 to 8 is considered good, 4 to 5 is fair, and 3 or below is poor (Foley et al., 2002). This review only accepted studies rated 4 or higher. If the study was only reported as an abstract, reviewers used the ‘PRISMA for Abstract Checklist’ (Beller et al., 2013). This review only included eligible abstracts containing at least 9/12 items (75%) from the Abstract Checklist as a threshold for quality. The reviewers were blinded to the cutoff values and any discrepancies in scoring were resolved in a consensus meeting.

2.5. Data extraction

Data was extracted from each article for the meta-analyses. Specifically, the extracted data included: patient characteristics (age, gender, stroke type); stimulation type, location, intensity and amount; outcome measures; and the sample size, group means, and standard deviations for each outcome. Where data was not provided, attempts were made to contact the corresponding author. In instances where results were only presented in figures and the authors did not report further information despite attempts to contact them, a Plot Digitizer program was used to extract values (Huwaldt, 2011). This program digitizes uploaded figures by calibrating the image's axes. Data points can then be extracted by clicking on any data point on the figure. If the study did not report enough quantifiable results and the authors did not respond to requests, then the study was excluded.

2.6. Statistical analyses

The process of selecting and screening studies relied on assessing the level of agreement between two raters, otherwise known as the Kappa coefficient. This statistic expresses percent agreement, accounting for chance. These calculations were performed on SAS software (SAS Institute Inc, 2010).

The effect of each study was calculated into an effect size index, a summary statistic indicative of the magnitude of a treatment effect. More specifically, the effect size refers to the standardized mean difference (SMD) of each study's results. Because problems can arise when small, non-parametric distributions are used with the traditional SMD called Cohen's *d*, this study used Hedges' (adjusted) *g*, which partially adjusts these problems. Hedge's g expresses the size of the intervention effect between two groups relative to the variability observed in that study (Deeks et al., 2008). It is useful when outcomes are non-parametric or measured in a variety of ways. For this review, the SMD (specifically, Hedges' adjusted *g*) was calculated using the following equations:

$$\mathrm{SMD}=f\frac{\overline{\mathrm{X}}_e-\overline{\mathrm{X}}c}{s}$$

Where $f=\frac{4(n_e+n_c-2)-4}{4(n_e+n_c-2)-1}$ And $S=\sqrt{\frac{(n_e-1)S_e^2+(n_c-1)S_c^2}{n_e+n_c-2}}$ (*e* = experimental group, *c* = control group, $\bar{x}$ = mean, *n* = number of subjects, *s* = standard deviation).

In interpreting effect size values, a rating scale for the SMD was used: less than 0.4 was small, 0.40–0.69 was moderate, and 0.70 or greater was large (Higgins and Green, 2008). In conjunction with effect size interpretations, a *p*-value of 0.05 or less was considered statistically significant. It must be noted, however, that the *p*-value is hindered by a small sample size and may conflate instances where an effect size is large but not significant in terms of a *p*-value. The discussion section contains attempts to explain such instances. There are limitations to using the SMD, but it is the recommended statistic of Cochrane reviews and is the most applicable statistic for these analyses.

The relevant study data (group sample size, group mean differences, and pooled standard deviations) were entered into RevMan 5, computer software used for performing meta-analyses and presenting the results graphically (Review Manager, 2014). In all studies, the outcome variables were treated continuously. Where not reported, standard deviations were calculated using SD = SE/($\sqrt{n}$) or using the PlotDigitizer. The pooled SD was calculated using:

$$n=\sqrt{\frac{(n_1-1)S_1^2+(n_1-1)S_2^2}{n_1+n_2-2}}$$

where n = number of subjects and s = standard deviation of groups 1 (experimental) and 2 (control).

To pool the effect sizes, RevMan was used to compute a weighted average of all of the studies' effect sizes. This weighted average will hereafter be referred to as the pooled effect size. This meta-analysis was performed using a random-effects model. The I^2 statistic, useful in suggesting how impacting the heterogeneity may be by describing the percentage of variation across studies, was used to assess statistical heterogeneity. Here, an I^2 less than 25%, 25–75%, and greater than 75% was regarded as low, moderate, and high, respectively (Higgins et al., 2003). Results were considered in light of the amount of the calculated statistical and clinical heterogeneity.

3. Results

3.1. Identification and selection of studies

Collectively, from all 13 databases, the search yielded a total of 1,549 studies. Using the RefWorks exact duplicate finder, the lead author excluded 559 duplicate studies (4 internal duplicates and 555 external duplicates). Thus, 990 studies were subjected to the initial screening. Two clinician reviewers, blinded from one another's results, included or excluded each of the 990 potential inclusions by screening titles and abstracts. The two screeners identified potential studies with 0.98 agreement (simple Kappa coefficient). The disputed citations (n = 6) were resolved with a meeting, resulting in 100% consensus of the 818 exclusions and leaving 172 studies. Upon further full-text review of the 172 studies, the lead author subsequently excluded 165 of them because they met certain exclusion criteria, data could not be extracted, or data was duplicated in another included study. A total of 7 studies (involving 8 trials) were ultimately identified for inclusion, demonstrated in Fig. 1. Kim et al. (2011) investigated 2 treatment arms, each with independent subjects in addition to a sham arm, thus contributing two trials and in this review. They are labeled A and B for the purposes of clarity.

3.2. Quality assessment

Two reviewers rated the quality of each of the included studies using the PEDro scale with 0.54 agreement. Disagreements were resolved in a consensus meeting and, after consultation with the PEDro scale authors, 100% agreement was achieved. The quality scores of the included clinical studies ranged from 4 to 9 (mean 6.13), which indicated a ‘good’ overall quality score for controlled clinical trials (see Table A1). No studies were excluded due to ‘poor’ quality (a PEDro score of 3 or less). No abstracts were included due to a lack of data and a lack of responses from authors, therefore the ‘PRISMA for Abstract Checklist’ was not used.

3.3. Description of studies

3.3.1. Participants—From all of the included studies, a total of 146 patients with post-stroke dysphagia received brain stimulation. About 55% of the participants were male (n = 81). The average age was 57.1 years old. All patients had suffered a stroke, the majority of which were ischemic strokes (n = 97 ischemic, n = 25 hemorrhagic, n = 20 other). The time

post-stroke varied greatly, from 24 h to 40 months. All subjects had some indication of dysphagia, although the severity was not elaborated upon other than baseline measures, and the method of dysphagia assessment also varied; two studies used clinical assessments and the five others used videofluoroscopy. Table A2 in the Appendix A provides more details.

Three studies investigated tDCS, totaling 50 patients who received this intervention ($n = 41$ ischemic, $n = 9$ hemorrhagic). Four studies investigated rTMS, totaling 92 patients who received this stimulation ($n = 56$ ischemic, $n = 16$ hemorrhagic, $n = 20$ other).

3.3.2. Outcomes—The outcome measures differed across trials (see Table A3). One of the most widely used scales in the field of dysphagia is the Penetration–Aspiration Scale (PAS), a scale of increasing severity from 1 to 8 (Rosenbek et al., 1996). Of the included trials for this meta-analysis, three used it as one of their outcome measures (Michou et al., 2014, Park et al., 2013; Kim et al., 2011). Of note, Michou et al. (2014) used the cumulative PAS scores for each subject. Another outcome measure, used by three trials (Michou et al., 2014; Park et al., 2013; Yang et al., 2012), was the functional dysphagia scale (FDS), a scale of increasing severity from 1 to 100 indicating various characteristics of the oral and pharyngeal stages, although two versions were used (Han et al., 2008; Han et al., 2001). Finally, the dysphagia outcome severity scale (DOSS; O'Neil et al., 1999), a scale of decreasing severity from 1 to 7, was used as an outcome measure for Kumar et al. (2011) and Shigematsu et al. (2013). This scale indicates diet, independence level, and type of nutrition. Khedr et al. (2009) used an outcome called the “dysphagic outcome severity scale” that appeared to be an unvalidated scale, different from the DOSS. The scale used by Khedr et al. (2009) rated patients on awareness of their dysphagia from 1 to 4 in increasing severity (Parker et al., 2004).

When there was more than one outcome, the outcome that was an ordinal scale was used as an attempt to maintain uniformity. Therefore, certain outcomes such as motor evoked potentials (MEPs) and timing measures were not analyzed because an ordinal scale was the preferred outcome to encourage similarity across studies. Further, because the directionality of the scales differed (i.e., a greater number on one scale indicates improvement whereas a greater number on another scale indicates decline), some effect sizes were multiplied by −1 to allow for uniformity of scale direction across all trials.

Lastly, outcome measures were made at different times. All studies recorded measurements at baseline, defined as the onset of the stimulation treatment, but the number of days of treatment varied from one session to 5 days to 10 days (5 consecutive days, 2 days off, then 5 more consecutive days). Three studies followed patients for long-term outcomes, which were also at varied time points (a fourth reported long-term outcomes but data point values could not be obtained). Even though the included trials lasted for different lengths of time, their “post-baseline measures” were grouped together and arbitrarily definedasless than one hour after the intervention ended. If a trial had an assessment at a time point greater than one hour after the intervention ended, those outcomes measures were defined as “long term” (see Table A4 in the Appendix A).

3.3.3. Electric field orientation and density—Table 1 highlights the details of each study's stimulation protocol. Studies using rTMS used widely different protocols. One

stimulated the unaffected hemisphere with high-frequency stimulation (5 Hz) at 90% of the resting threshold (Park et al., 2013). One stimulated the affected hemisphere at 5 Hz at 100% and the other stimulated the unaffected hemisphere with low-frequency stimulation (1 Hz) at 100% (Kim et al., 2011). Another stimulated the affected hemisphere with high-frequency stimulation (3 Hz) at 120% (Khedr et al., 2009). And the most recent study stimulated the unaffected hemisphere with high-frequency stimulation (5 Hz) at 90% of the resting motor threshold (Michou et al., 2014). The coil was nearly the same size and same figure-8 shape across all rTMS studies. The studies report targeting cortical areas including the pharyngeal, mylohyoid, and esophageal motor cortex.

Two of the three tDCS studies stimulated the affected hemi-sphere,bothat 1 mA. The study that stimulated the unaffected hemi-sphere used 2 mA of voltage. The targeted cortical area for these three studies was the “swallowing motorcortex”or the “pharyngeal motor cortex.” This area is assumed to refer to the midinferior lateral section of the primary motor cortex, as reported by the respective authors(Table 1). The size and placement of the anodal and reference electrodes were similar across the three studies.

3.3.4. Duration of stimulation—The duration of stimulation varied from 1 to 10 days of treatment with 10–30 min of stimulation each day (Table 1). No author provided a rationale for the selected regimen.

3.4. Synthesized data analyses

3.4.1. Overall summary effect—There is an overall significant, moderate size of effect in favor of transcranial neurostimulation on post-stroke dysphagia (pooled effect size = 0.55; 95% CI = 0.17, 0.93; $p = 0.004$, see Fig. 2). The statistical heterogeneity of the combined trials is considered low, $I^2 = 20\%$.

Three studies were found to have small, negative effect sizes (Michou et al., 2014; Yang et al., 2012; Kim et al., 2011). Five studies had moderate to large, positive effect sizes ranging from 0.55 to 1.15 but only two were considered statistically significant (see Table 2).

3.4.2. Stimulation type—Subgroup analyses were performed to look for emerging factors. When considering the three tDCS trials alone, there was a moderate but non-significant pooled effect size (0.52, $p = 0.12$) favoring the stimulation intervention (Fig. 3A). The five trials investigating rTMS on post-stroke dysphagia demonstrated a similar, but significant, pooled effect size (0.56, $p = 0.03$; see Fig. 3B).

3.4.3. Affected vs. unaffected hemispheric stimulation—Studies using non-invasive brain stimulation, either rTMS or tDCS, to the affected (lesioned) hemisphere demonstrated a moderate yet non-significant pooled effect size of 0.46 ($p = 0.16$) across the four applicable trials (Fig. 4A). The four studies that stimulated the unaffected (contralesional) hemisphere demonstrated a moderate and significant pooled effect size (0.65; $p = 0.01$), seen in Fig. 4B. The trials stimulating the unaffected hemisphere had considerably less statistical heterogeneity ($I^2 = 0\%$) than those stimulating the affected hemisphere ($I^2 = 51\%$).

3.4.4. Stimulation duration—This meta-analysis found brain stimulation lasting 10 minutes or less to have a similar, moderate but non-significant pooled effect size (0.64; 95% CI = -0.02,1.29; $p = 0.06$) when compared to stimulation lasting 20 to 30 min (0.49; 95% CI =−0.02,1.01; $p = 0.06$). These subgroups are demonstrated in Figs. 5A and B and have moderate statistical heterogeneity (I^2 = 28% and 30%, respectively).

3.4.5. Long-term follow-up—Only three trials followed patients for what was considered to be long-term follow-up (Fig. 6). Park et al. (2013) re-assessed patients at 2 weeks and found a moderate but non-significant effect size still in place (SMD = 0.38). This is just slightly less than the study's immediate effect size of 0.55. Yang et al. (2012) demonstrated a small, non-significant effect size of 0.37 at their 3-month follow-up, contrasting with the negative effect size of −0.13 seen immediately after stimulation. Finally, Shigematsu et al. (2013) showed a very large and significant effect size of 1.74 when they re-assessed patients at 1 month. All together, these studies suggest that the pooled effects of non-invasive brain stimulation were large at long-term follow-up (0.81; 95% CI = −0.06, 1.68). This result should be considered in light of moderate heterogeneity (I^2 = 54%) and a lack of statistical significance ($p = 0.07$).

4. Discussion

Post-stroke dysphagia is not only costly, but potentially fatal and is experienced in at least one out of every two stroke patients. Many studies have investigated whether non-invasive brain stimulation could be used as a treatment to rehabilitate dysphagia. Randomized controlled trials that have investigated non-invasive brain stimulation as a treatment for stroke-related dysphagia have been small and therefore inadequate in providing reliable estimates of treatment effects on their own. A systematic review is very helpful in this context to synthesize the results from these trials and to sum up the best available research on this topic. However, no review to date has specifically synthesized the effects of non-invasive brain stimulation on post-stroke dysphagia. The purpose of this systematic review and meta-analysis was to summarize and synthesize the findings of the best evidence, to date.

Seven randomized controlled trials met this review's inclusion and exclusion criteria. One trial contained two eligible treatment arms done on independent subjects. Thus, eight trials were included. The synthesized findings demonstrate that the use of non-invasive brain stimulation facilitated recovery in post-stroke dysphagia. When combining the 8 trials, a moderate and significant pooled effect size emerged (0.55, 95% CI = 0.17, 0.93; $p = 0.004$). This meta-analysis standardized outcomes and combined multiple small studies, allowing for a bigger picture: in 95 out of 100 meta-analyses done on this very same research question, one should expect to see an effect size of an improvement in dysphagia ranging from 0.17 to 0.93.

The pooled effect size of 0.55 reached significance and is much greater than what has been seen in other meta-analyses of motor studies of the limbs. Two recent meta-analyses found smaller and non-significant effect sizes when pooling data from anodal transcranial direct current stimulation on post-stroke motor performance (Marquez et al., 2013; Bastani and

Jaberzadeh, 2012). They both calculated non-significant effect sizes of 0.05 and 0.39, respectively. The larger effect size from the present study may have to do with the bilateral cortical representation of swallowing, where it is possible to exploit the relatively intact networks in the unlesioned hemisphere for plastic changes. This study also highlights several factors that emerged across trial outcomes, discussed below.

4.1. tDCS vs. rTMS

One factor to consider is the type of stimulation: transcranial direct current stimulation (tDCS) versus repetitive transcranial magnetic stimulation (rTMS). This is the first study to compare the two techniques in a quantitative manner as a means to address the question: Which type of stimulation should be used? Here, tDCS and rTMS showed similar pooled effect sizes on swallowing outcomes (0.52 and 0.56, respectively), but there are too many differences across study designs to draw any definitive conclusions. The question should also be posed in a clinical light: Which type of stimulation should be used for which patient? To answer this question, neurophysiological outcomes and patient characteristics must be carefully considered. Unfortunately, the evidence in the extant literature is not abundant enough to address this important question. The only conclusion that this review can make is that, considering the technique differences and confounding variables, no evidence emerged to suggest major differences in efficacy between the two techniques.

One variable confounding these findings is hemispheric stimulation discussed below in 4.2. The pooled effect size for all tDCS studies was 0.52 but when excluding the 1 study that stimulated the affected hemisphere, the effect size jumped to 0.85 (95% CI = 0.14, 1.56; p = 0.02). For rTMS studies, excluding the 2 studies that stimulated the affected hemisphere changed the effect size very little from 0.56 to 0.59 (95% CI = −0.02, 1.20; p = 0.06). Thus, when controlling for hemispheric stimulation, tDCS studies demonstrated a larger and significant effect size than rTMS studies. One possible explanation is that tDCS activates a larger cortical area thereby stimulating more of the swallowing cortical network.

4.2. Hemispheric stimulation

Another important factor is the issue of which hemisphere to stimulate. Trials stimulating the unaffected hemisphere demonstrated a slightly larger, and significant, pooled effect size than trials stimulating the affected hemisphere (see Fig. 4). Though the unaffected hemisphere's effect size (0.65, p = 0.01) and the affected hemisphere's effect size (0.46, p = 0.16) are both interpreted as moderate, the larger effect size for the unaffected hemisphere is supported by a significant p-value and a low heterogeneity score (I^2 = 0%), indicating true intervention effect when compared to the affected side (I^2 = 51%). This result is further supported by the findings of earlier studies that also found an increase in the strength of the unaffected hemisphere helps to rehabilitate swallowing function (Mistry et al., 2012; Teismann et al., 2011; Singh et al., 2009; Hamdy et al., 1998b). Further, Kumar and colleagues (2011) suggest that non-invasive brain stimulation may be an “augmentation effect of the naturally occurring changes in the unaffected swallowing cortex” (2011, p. 1038). Swallowing is bilaterally innervated and plasticity of the unaffected hemisphere likely facilitates recovery of the swallow.

Khedr et al. (2009) followed 10 of their enrolled subjects who received rTMS (not sham) and at 1-month post-stimulation found significant increases in the excitability of the corticobulbar projections in *both* hemispheres despite stimulation to only the affected hemisphere. Similarly, one subject in Yang and colleague's (2012) study demonstrated an increase in glucose metabolism in the unaffected hemisphere despite stimulation to the affected hemisphere. As Hamdy and colleagues demonstrated (1998b), an increased cortical representation of the swallowing mechanism in the unaffected hemisphere is associated with recovery of the swallow.

The present review corroborates these results mentioned above and two of the trials best exemplify this point. They were performed using the same excitatory stimulation (5 Hz rTMS for 10 days at 90–100% of resting motor threshold) on very similar populations (an average age of late 60's to early 70's, time post-stoke both averaged from 1 to 2 months post-onset) with the same outcome (Penetration–Aspiration Scale [PAS] assessed by videofluoroscopy). The main difference between the two studies was the hemispheric stimulation. Kim et al. (2011a) stimulated the affected hemisphere while Park et al. (2013) stimulated the unaffected hemisphere. Their effect sizes mimic that found in the overall meta-analysis: stimulating the unaffected hemisphere produced a larger magnitude of improvement in dysphagia (lower PAS scores) than stimulating the affected hemisphere (Figure A5). However, other variables likely played a role in the opposing outcomes. One such variable is stimulation duration. Kim et al. (2011) stimulated for 20 min per day while Park et al. (2013) stimulated for 10 min per day. This interesting confounder is discussed further in Section 4.3. Other variables that likely affected the outcome are: lesion type, location, and size, stroke type, and study methodological design (a 4/10 versus a 9/10 on the PEDro scale, respectively).

It should be noted that Corti, Patten, and Triggs conducted a review in 2012 of rTMS on the motor cortex in post-stroke patients, concluding that excitatory stimulation to the affected hemisphere is an effective approach. Two important differences may explain the discrepancies found between their review and the present review. One, they included non-controlled studies, which contain bias due to a lack of a control group. Two, they analyzed motor outcomes of the arm and hand. Swallowing follows a more complex system of bilateral innervation than the unilateral corticospinal pathways. These two reasons may explain the contrasting results.

Another issue related to hemispheric stimulation is excitatory versus inhibitory stimulation. Only one study (Kim et al., 2011b) used inhibitory stimulation to the unaffected hemisphere and they showed positive results (see Fig. 4B). Authors have suggested that up-regulation of the unaffected hemisphere will increase pharyngeal representation at that stimulation site thereby improving the swallow (Park et al., 2013; Kumar et al., 2011; Hamdy et al., 1998b). Other authors have introduced down-regulation of the unaffected hemisphere to purportedly decreased transcallosal inhibition, thus improving swallowing function (Verin and Leroi, 2009) and other motor movements such as hand strength (Ludemann-Podubecka et al., 2014; Marquez et al., 2013). The limited results of the present review suggest that both excitatory and inhibitory stimulation of the unaffected hemisphere improve dysphagia, although more

research is required. Larger RCTs will be informative for furthering the understanding of the mechanisms behind non-invasive brain stimulation.

4.3. Stimulation duration

This review also looked at the effect of stimulation duration. Overall, there was little difference in size of effect between trials that stimulated for 10 min or less and those that stimulated for 20–30 min (Fig. 5). However, conclusions should not be drawn from this result due to the multitude of confounding variables. What is valuable, on the other hand, is what was expected to be seen and why it's not apparent.

Previous studies show that more stimulation is not necessarily better. Over activation of N-methyl-D-aspartate (NMDA) after stroke, especially in the early stages, may be detrimental (Adeyemo et al., 2012). Other studies have documented ceiling effects and an eventual decrease in MEP amplitude with prolonged stimulation (Batsikadze et al., 2013; Monte-Silva et al., 2013). Therefore, one may expect to see smaller or reversed effects with longer stimulation.

On the other hand, some researchers conclude that greater stimulation for longer duration is needed for dysphagia recovery. Yang et al. (2012) stimulated with anodal tDCS at 1 mA for 20 min per day for 10 days and saw no difference between their stimulation and sham group at post-baseline. They concluded that longer stimulation like 30 minutes per day by Kumar et al. (2011) resulted in more positive results because their study used the same electrode placements with anodal tDCS at 2 mA for 30 min per day for 5 days. While it is tempting to make conclusions here about stimulation intensity and duration, multiple variables preclude such inferences. For one, the authors of the two studies stimulated different hemispheres. Further, the protocols also differed in patient-specific electrode positioning, lesion size, and outcome scales. Therefore it is difficult to make conclusions about stimulation duration from the present studies due to their differences.

In the bigger picture, one could argue that tDCS and rTMS should not be grouped together to address stimulation duration, as was done in the present review. They require different amounts of time to create certain responses. And perhaps this is the reason for the null outcome. Evaluation for duration should be stratified by treatment modality, but there is currently not enough data to analyze it in this fashion. Therefore these results do not shed light on how stimulation duration relates to outcomes in post-stroke dysphagia, but rather bring to light variables that should be considered in future research.

4.4. Long-term follow-up

This review found three studies that investigated long-term efficacy. Clinically, this is the most important implication of non-invasive brain stimulation. Patients need to improve their swallow not only immediately after the stimulation session but in the long-term, as well. It is difficult to draw conclusions from the three small trials that present conflicting results at different time points post-stimulation (2 weeks, 1 month, 3 months, see Fig. 6), as well as moderate statistical heterogeneity. The three trials' effect sizes were small to large in magnitude, although only one out of the three studies was statistically significant (Shigematsu et al., 2013). Another meta-analysis found similar mixed results at follow-up on

motor function in stroke patients; only 2 out of the 4 studies reported significant long-term improvements (Marquez et al., 2013).

Literature supports the theory that non-invasive brain stimulation increases synapse transmission strength and rate lasting beyond treatment sessions. While it is tempting to highlight all three positive effect sizes from the included trials, the one statistically significant trial may have skewed the overall pooled effect size (see Fig. 6). Therefore the general result of this subgroup does not definitely support long-term effects of transcranial neurostimulation. Rather, a non-significant trend was seen in the direction of a positive effect size. If there is, indeed, a long-term effect, then the use of non-invasive brain stimulation on healthy subjects should be questioned (Doeltgen, 2014; Ridding and Rothwell, 2007). Little is known about the difference in plasticity between healthy subjects and stroke patients and what variables influence the outcomes. There is a need for more data.

4.5. Strengths and limitations

4.5.1. Strengths—This review included an extensive search of 13 databases, including grey literature, without limitations on language or publication date. The inclusion and exclusion criteria were defined a priori and the review's focus was appropriately narrow. The authors aimed to include only good-quality studies by using RCTs and systematically rating each one. Further, this review is the first to estimate an overall effect of non-invasive brain stimulation on post-stroke dysphagia while highlighting important factors for consideration.

Publication bias is an important consideration in meta-analyses to assess for any bias toward significant results. Such an analysis can be performed with a simple funnel plot. Publication bias is suggested by asymmetry around the pooled effect size, usually in a positive direction. Here, the studies lie somewhat symmetrically around the pooled effect size, indicated by the vertical line in Fig. 7, suggesting little publication bias in this review.

4.5.2. Limitations—There are multiple limitations that must be addressed. First, the included studies were heterogeneous in their treatment protocol and outcome measurements. One study in particular, Khedr et al. (2009), may have shown such a large effect size due to several factors influencing the precision of their results. One, the outcome was an unvalidated scale measuring patient awareness of dysphagia, and two, they targeted the swallowing motor cortex by measuring esophageal motor-evoked potentials. Additionally, the Plot Digitizer was used to extract the post-baseline values and standard deviations. In these ways it is possible that the study's effect size is not a precise estimate of their stimulation treatment, especially considering their results, which greatly contrast other studies that stimulated the affected hemisphere. However, when excluding this study from the analysis, the pooled effect size only slightly dropped from 0.55 to 0.44 –still considered moderate– and remained significant ($p = 0.02$).

Second, patient characteristics differed across studies. Stroke type (ischemic and hemorrhagic) and time post-onset (combining acute and chronic stroke patients) are just a few of the diverse variables that could have confounded the results. However, no matter what the lesion type, it is presumed that the dysphagias were neurogenic and therefore should

benefit from interventions promoting neuroplasticity. Kim et al. (2011) included 2 subjects with traumatic brain injury, which was exclusionary criterion. It was the judgment of the lead author to allow the study to remain due to the strength of this study, overall.

Third, some studies combined the non-invasive brain stimulation with other actions (i.e., pharyngeal electrical stimulation, an effortful swallow). This review did not exclude any randomized controlled trial if it provided paired stimulation. Certainly, by combining the stimulation with another form of intervention, a confounding variable comes into play: the type and strength of the secondary action. While some research has demonstrated that paired stimulation recovers function better than one intervention used alone, this does not take away from the weight of evidence indicating the benefit of neurostimulation (Michou et al., 2012; Celnik et al., 2009). Future research should continue to investigate how, and which, paired interventions work optimally in recovering swallowing function in the patient.

Finally, it is useful to discuss factors in the studies that did not favor stimulation (Michou et al., 2014; Yang et al., 2012; Kim et al., 2011). These three studies had a near-zero effect size, suggesting that there was no difference in the magnitude of effect between the stimulation group and the control group. Two of the studies received a low PEDro score of 4, suggesting only ‘fair’ methodological quality. Yang et al. (2012) used swallowing training that varied depending on each patient's swallowing function. Michou et al. (2014) showed no effect size, however this study reported only one session of treatment. One session may not be enough to register a measureable benefit to the patient. These factors should be considered when these three studies are grouped with the other studies in this analysis. In fact, when these three studies are removed from the overall analysis, the measure of variability due to heterogeneity rather than chance (the I^2 statistic) drops from 20% to 0% and the effect size jumps from 0.55 to 0.91, suggesting that these three studies may be limiting a more accurate effect size. However, these studies did meet all of the eligibility criteria and deserve more reflection in light of an intervention that is still not fully understood.

4.6. Conclusion

This review found evidence for the efficacy of non-invasive brain stimulation on post-stroke dysphagia but larger randomized-controlled trials are needed to better understand its effect on post-stroke dysphagia. Future studies should enroll a large, homogeneous population and be well controlled. Researchers should pay careful attention to which hemisphere they select to stimulate and what outcome measures best address their research question. Studies would benefit from documenting neurophysiological outcomes that may provide insight into the behavioral changes. Other research questions may want to consider if non-invasive brain stimulation is best for their patient and why. For instance, peripheral electrical stimulation (PES) has also shown promising results (Michou et al., 2014).

Many may wonder if non-invasive brain stimulation is ready to be used clinically. While this is not the question addressed by the present review, the authors believe the answer is no for two reasons. One, while the results of this review are generally in favor of non-invasive brain stimulation, specific and definitive conclusions cannot be made from only eight small and clinically heterogeneous trials. Two, there are not enough safety measures in place for the

intervention to become a clinical tool. Even though no studies demonstrated statistically significant negative effect sizes or adverse outcomes, safety measures need to be more fully developed and put in place to protect patients before non-invasive brain stimulation can be considered for clinical use. Based on this preliminary review, non-invasive brain stimulation facilitated recovery in post-stroke dysphagia but, in our opinion, should not yet be considered for clinical use outside of clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This manuscript is based on research conducted by Jessica M. Pisegna, a PhD candidate at Boston University, Boston, MA. This project had no external funding. We are grateful to Lisa Philpotts for teaching us her expert methods in systematic searching. The authors would also like to thank Marika Muttilainen for participating in the screening process.

All authors, except for the second author, receive partial salary funding by the fourth author's NIH grant, NIDCD 1R01DC012584-01A1. Research reported in this publication/presentation was supported by the National Institute On Deafness And Other Communication Disorders of the National Institutes of Health under Award Number R01DC012584. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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highlights

- We synthesize evidence for non-invasive brain stimulation on post-stroke dysphagia.
- Transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation
- (rTMS) significantly increased swallowing outcomes in stroke patients. Stimulating the unaffected hemisphere resulted in a significant pooled effect size.

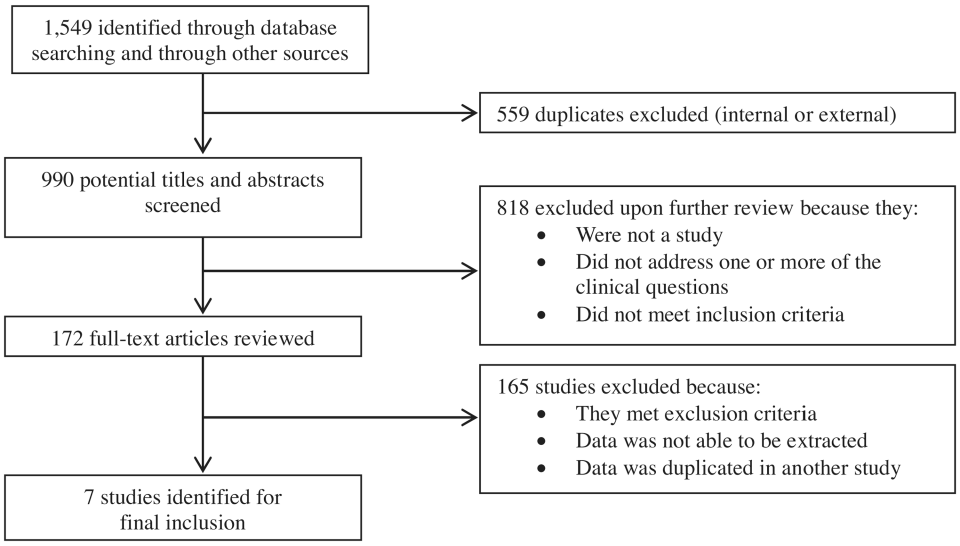

Fig. 1.

Process for identification of included studies (PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

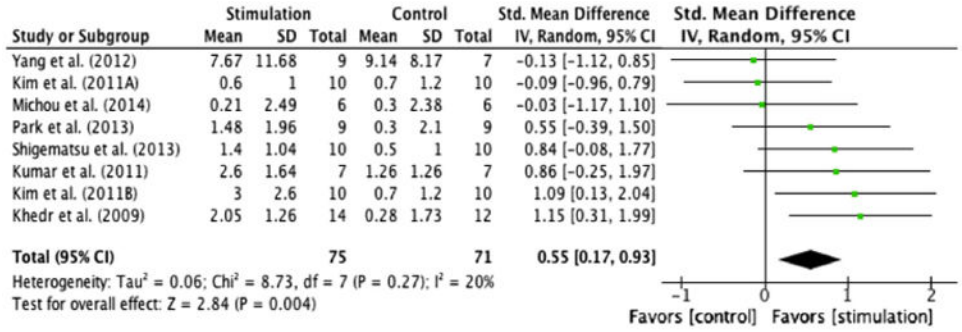

Fig. 2.

Calculated effect sizes (standardized mean differences) from baseline to post-baseline of all included trials and the total pooled effect size of all trials combined. ‘Mean’ represents post values minus baseline; ‘SD’ (standard deviation) represents baseline SD and post SD pooled together; ‘Total’ indicates the number of subjects in each group. Forest plot: the size of the green square indicates sample size and is crossed by a line indicating the 95% confidence interval (CI); The large black diamond is the pooled estimate of effect size of all trials combined; The effects sizes of 5 of the 7 studies had to be multiplied by −1 to adjust for directionality of their outcome scales (all but Kumar et al. (2011) and Shigematsu et al. (2013)); Kim et al. (2011) investigated 2 treatments arms in addition to a sham arm, A: high-frequency stimulation to the affected hemisphere and B: low-frequency stimulation to the unaffected hemisphere on independent subjects.

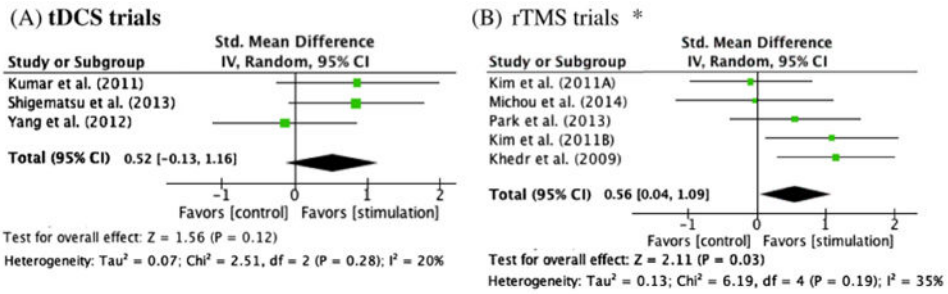

Fig. 3.

(A) Effect sizes of tDCS trials on post-stroke dysphagia; (B) Effect sizes of rTMS trials on post-stroke dysphagia. Forest plots: the green square size indicates sample size and is crossed by a line indicating the 95% confidence interval (CI); The large black diamond is the pooled effect size of the combined trials; The effects sizes of all studies (but Kumar et al. (2011) and Shigematsu et al. (2013)) were multiplied by −1 to adjust for directionality of their outcome scales; *Kim et al. (2011) investigated 2 treatments arms in addition to a sham arm, A: high-frequency stimulation to the affected hemisphere and B: low-frequency stimulation to the unaffected hemisphere on independent subjects. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

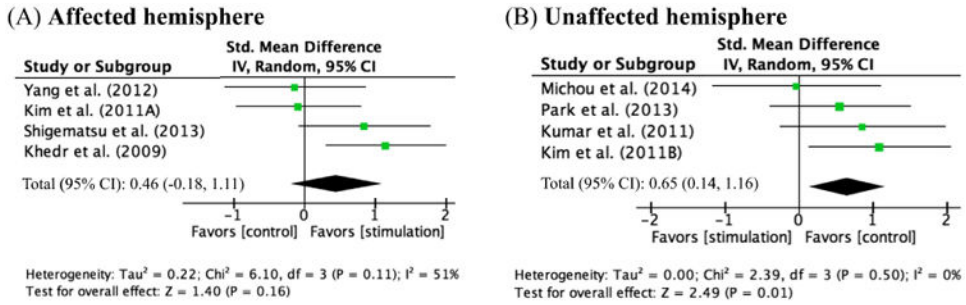

Fig. 4.

(A) Effect sizes of studies stimulating the affected (lesioned) hemisphere and their pooled effect size; (B) Effect sizes of studies stimulating the unaffected (contralesional) hemisphere and their pooled effect size. Forest plots: the green square size indicates sample size and is crossed by a line indicating the 95% confidence interval (CI); The large black diamond is the pooled effect size of the combined trials; The effects sizes of all studies (but Kumar et al. (2011) and Shigematsu et al. (2013)) were multiplied by −1 to adjust for directionality of their outcome scales; *Kim et al. (2011) investigated 2 treatments arms in addition to a sham arm, A: high-frequency stimulation to the affected hemisphere and B: low-frequency stimulation to the unaffected hemisphere on independent subjects. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

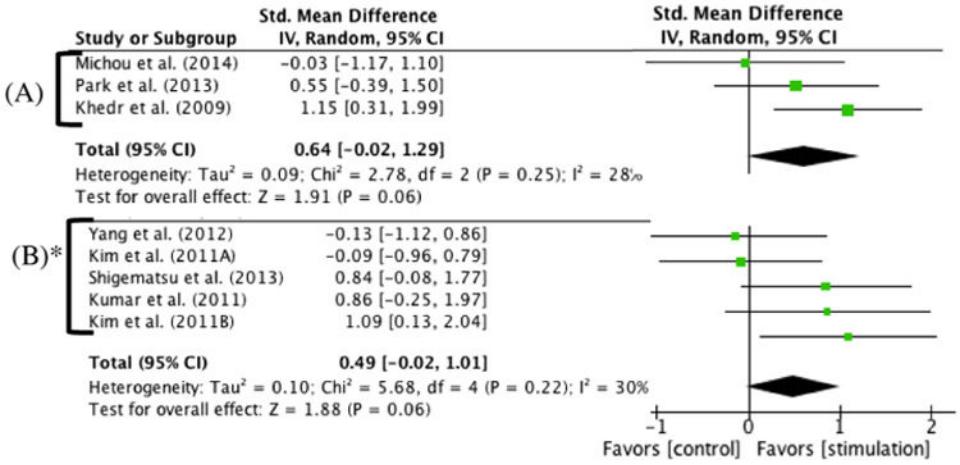

Fig. 5.

Effect sizes of trials that provided (A) about 10 min or less of stimulation; (B) 20–30 min of stimulation and the pooled effect size of each group. Forest plots: the green square size indicates sample size and is crossed by a line indicating the 95% confidence interval (CI); The large black diamond is the pooled effect size of the combined trials; The effects sizes of all studies (but Kumar et al. (2011) and Shigematsu et al. (2013)) were multiplied by −1 to adjust for directionality of their outcome scales; *Kim et al. (2011) investigated 2 treatments arms in addition to a sham arm, A: high-frequency stimulation to the affected hemisphere and B: low-frequency stimulation to the unaffected hemisphere on independent subjects. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

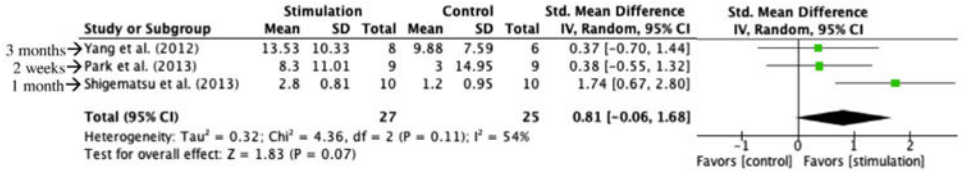

Fig. 6.

Effect sizes at long-term follow-up. Forest plots: the green square size indicates sample size and is crossed by a line indicating the 95% confidence interval (CI); The large black diamond is the pooled effect size of the combined trials; The effects sizes of Yang et al., 2012 and Park et al., 2013 were multiplied by −1 to adjust for directionality of their outcome scales. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

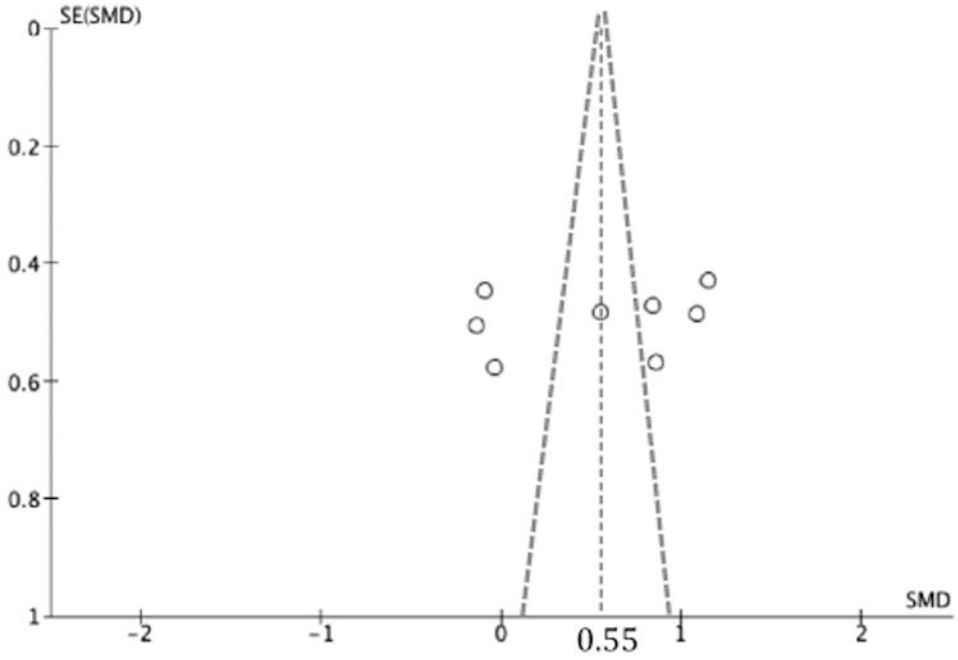

Fig. 7.

Funnel plot of the 8 included trials assessing publication bias. SE = Standard error, SMD = Standardized mean difference.

Table 1

Parameters of stimulation type, schedule, intensity, and location from all included trials.

Study	Stimulation	Schedule	Hemisphere	Location	Size
Michou et al. (2014)	rTMS	- 1 day - 5 blocks of 50 pulses - 5 Hz at 90%	Unaffected *	Pharyngeal motor cortex	70 mm figure-8 coil
Park et al. (2013)	rTMS	- 10 days, 10 min/day - 10 blocks of 50 pulses - 5 Hz at 90%	Unaffected	Pharyngeal cortical “hot spot”	70 mm figure-8 coil
Kim et al. (2011)	rTMS (3 groups)	- 10 days, 20 min/day - (A) High: 5 Hz 100%20 blocks of 50 pulses - (B) Low: 1 Hz 100%1 block of 1200 pulses	(A) Affected (B) Unaffected Sham: Affected	Mylohyoid cortical “hot spot”	90 mm figure-8 coil
Khedr et al. (2009)	rTMS	- 5 days, 10 min/day - 10 blocks of 30 pulses - 3 Hz at 120%	Affected	Esophageal motor cortex	90 mm figure-8 coil
Shigematsu et al. (2013)	tDCS	- 10 days, 20 min/day - 1 mA anodal	Affected	Pharyngeal motor cortex	5 × 7 cm^2 (both electrodes)
Yang et al. (2012)	tDCS	- 10 days, 20 min/day - 1 mA anodal	Affected	Pharyngeal motor cortex	5 × 5 cm^2 (both electrodes)
Kumar et al. (2011)	tDCS	- 5 days, 30 min/day - 2 mA anodal	Unaffected	Swallowing motor cortex	Anode: 3 × 5 cm^2 Referent: 5 × 6 cm^2

rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; % reported under Schedule is that of resting motor threshold.

* Protocol references Jefferson et al. (2009); confirmed via personal communication with lead author (March 2, 2015).

Table 2

Calculated effect sizes (standardized mean differences) of included studies and their designated magnitudes.

Study	Effect size	95% CI	Magnitude[+]
Yang et al. (2012)	−0.13	(−1.12, 0.85)	Small
Kim et al. (2011)$_{\text{HIGH FREQ}}$	−0.09	(−0.96, 0.79)	Small
Michou et al. (2014)	−0.03	(−1.17, 1.10)	Small
Park et al. (2013)	0.55	(−0.39, 1.50)	Moderate
Shigematsu et al. (2013)	0.84	(−0.08, 1.77)	Large
Kumar et al. (2011)	0.86	(−0.25, 1.97)	Large
Kim et al. (2011)$_{\text{LOW FREQ}}$	1.09 *	(0.13, 2.04)	Large
Khedr et al. (2009)	1.15 *	(0.31, 1.99)	Large
	Pooled = 0.55	(0.17, 0.93)	

[+] Higgins and Green, 2008; CI, confidence interval; SMD, standardized mean difference.

* These two studies were the only significant effect sizes, as their confidence intervals did not include zero.