# Accepted Manuscript


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PII: S0149-7634(18)30874-1
DOI: https://doi.org/10.1016/j.neubiorev.2019.04.019
Reference: NBR 3404

To appear in:

Received date: 14 November 2018
Revised date: 12 March 2019
Accepted date: 24 April 2019

Please cite this article as: Bucur M, Papagno C, Are transcranial brain stimulation effects long-lasting in post-stroke aphasia? A comparative systematic review and meta-analysis on naming performance, *Neuroscience and Biobehavioral Reviews* (2019), https://doi.org/10.1016/j.neubiorev.2019.04.019

**Are transcranial brain stimulation effects long-lasting in post-stroke aphasia? A comparative systematic review and meta-analysis on naming performance.**

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Highlights

- This is the first meta-analysis of NIBS long-term efficacy for post-stroke aphasia
- Both tDCS and rTMS treatment effects remain stable between 1 and 6 months
- rTMS coupled with SLT can be considered effective for chronic and subacute aphasia
- There is controversial evidence of tDCS effects in aphasia treatment
- The GRADE level of evidence was moderate for rTMS and low for tDCS studies

**Abstract**

In the last decade, the effects of NIBS on language recovery in post-stroke aphasia have been evaluated, but little is known about the long-term effectiveness.

To this aim, we conducted a systematic review and meta-analysis to determine whether positive effects, mainly on naming performance, are maintained in time, and rTMS and/or tDCS (either as an add-on therapy to SLT or as monotherapy) can be considered effective and reliable interventions for naming rehabilitation.

Sixteen studies met our inclusion criteria and the pooled SMDs showed a medium to large rTMS effect and a small to medium tDCS effect. Critically, the treatment effects were maintained in time. Sub-analyses indicated that while rTMS can be considered effective for both subacute and chronic patients,

tDCS seems adequate only for chronic aphasia. Importantly, the level of evidence as qualified with GRADE was moderate to high for rTMS and low for tDCS studies.

KEYWORDS: post-stroke aphasia; tDCS; rTMS; noninvasive brain stimulation; stroke; language rehabilitation, follow-up, naming, GRADE

## 1. Introduction

Stroke is the most disabling health condition worldwide in adulthood and a substantial proportion of stroke survivors live with aphasia [1]. Post-stroke aphasia is an acquired language disorder and one of the worst outcomes of stroke, altering some or all modalities of language processing: speech, reading, and writing. The most common causes are left middle cerebral artery infarcts with damage to the cortical and subcortical regions in the left hemisphere; rarely aphasia is due to a right hemisphere lesion. Linguistic impairment can vary, differing in production fluency and level of comprehension, repetition, and word retrieval ability. Symptoms are heterogeneous and can change over time; for instance, patients having one type of aphasia in the acute phase may present a different clinical profile in the chronic phase[2].

It is estimated that more than 15 million people worldwide suffer from stroke each year [3], aphasia being present in approximately 38% of stroke survivors [1,4]. Due to early physiological repair mechanisms involving cell genesis, axon growth, and synaptic modulation, the majority of stroke patients achieve some spontaneous recovery, even in the absence of a rehabilitation treatment. Nevertheless, around 40% of these patients still have significant aphasia one year after stroke and residual symptoms may persist for many years [5,6].

The economic and social consequences are highly relevant since aphasia has a negative impact on activities of daily living and on people's quality of life [7]. Patients with reduced speech and comprehension abilities are more likely to suffer from mood disorders such as depression, social isolation, unemployment, which compromise their psychological wellbeing and put major burdens on their caregivers and on the health-care system [8,9]. These patients experience longer hospitalization periods, need more intensive health service support, participate in fewer activities and report high distress [10].

Current research demonstrates that aphasia recovery is modulated by many variables including lesion size and site, aphasia type and severity and, to some extent, by the nature of early hemodynamic response, type of treatment, interval between onset and beginning of speech therapy, environmental support etc. [11]. After the initial spontaneous recovery following stroke (e.g., blood flow stabilization, resolution of brain swelling), recovery relies on the reorganization of brain networks, which occurs both spontaneously and in response to behavioral training (e.g., speech-language therapy) [12].

The most widespread current rehabilitation approach for aphasia is speech and language therapy (SLT) [13]. SLT has been proved to reduce language impairment, but treatment is quite expensive, progress is often slow, and effect sizes are sometimes modest [14]. Even though the degree of spontaneous recovery gradually declines during the first 6–12 months, it is well established that at least partial recovery of language can be reached at any point after stroke, but requires a large amount of time and therapy sessions ("more is better"). A recent study [15] found no added value from more than two hours of daily SLT therapy but instead showed that an increase in treatment duration (even only 2 weeks) contributes significantly to recovery. Unfortunately, because of the limited clinical resources many patients do not receive the recommended amount of training that was estimated at 98.4 hours of therapy [16–18].

In an attempt to manipulate the neurotransmitter systems and subsequently facilitate language recovery, different drugs such as memantine, vasopressin, dextroamphetamine, and piracetam, have been tried [19,20]. To date, the findings supporting pharmacological therapy are questionable [21].

In this context, alternative methods for increasing aphasia treatment effectiveness, by either improving the total amount of learning achieved (better results) or by speeding up the learning process (faster results), have been investigated. There is evidence for structural and functional reorganization of

language networks after stroke that mediates recovery, and recent research on brain plasticity [22,23] has led to new approaches in stroke rehabilitation. The improvement of aphasia is associated with the reorganization of the balance between the perilesional ipsilateral and contralateral hemispheric activation [24,25]. Additional therapies, with or without SLT, like noninvasive brain stimulation (NIBS) interventions, have been tried in order to modify the cortical excitability and therefore promote the post-stroke reorganization of language networks [26].

The most extensively applied protocols in post-stroke aphasia rehabilitation research are based on repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). Although both rTMS and tDCS are non-invasive stimulation techniques, their functioning principles, and consequently their effects differ; while rTMS induces action potentials in neuronal axons via electromagnetic current, tDCS modulates neural firing rates due to current-induced changes in resting membrane potentials [27–31]. For a more general overview and background regarding the rTMS and tDCS mechanisms, see [23,29,32–34]; for example, Krause et al. [35]'s data indicate that tDCS may act by altering functional connectivity, both locally and between distant brain areas.

TMS and tDCS can excite or inhibit neuronal populations, depending on the stimulation parameters (e.g., high-frequency vs low-frequency rTMS, cathodal vs anodal tDCS), that can last for many minutes after a short session. Equally important, all these factors interact with several other variables related to individual anatomy (e.g., properties of the brain tissue and its location), and the brain's internal state at the time of stimulation, i.e., the initial neural activation state and synaptic plasticity of the stimulated area. In particular, tDCS will affect the performance (improving or decreasing it) depending on the state of the neural population of the stimulated area; being a neuromodulatory technique, it induces firing of neurons that are near threshold while those neurons not activated by the task are less likely to discharge (for details on state-dependent brain stimulation see [36,37]).

Research shows that post-stroke neuronal reorganization may be beneficial or maladaptive [38] and tDCS and rTMS could have a therapeutic role by potentially reversing an eventual maladaptive pattern of activation and by creating long-lasting desirable brain changes.

The possibility to modulate brain plasticity by means of rTMS and tDCS and consequently affect behavior opens up new possibilities in this field, but to date, there is still a great deal of uncertainty about the effects of different stimulation parameters and protocols (e.g., inhibitory - decreasing activation in the intact hemisphere, or excitatory - increasing the output of the perilesional region in the damaged hemisphere).

Reviews of tDCS, rTMS and aphasia literature are disproportionately numerous when compared with the number of original experimental studies [39–53]. For example, Wortman-Jutt and Edwards [20] showed that between 2008 and 2015, 48% of publications regarding tDCS and aphasia rehabilitation were review papers. This indicates the huge interest in this topic but also the difficulty in conducting experimental research (i) on a clinical population characterized by great variability (especially regarding lesion type and clinical picture), (ii) in the absence of solid data regarding the underlying mechanisms of these techniques, i.e., without being able to make predictions on their clinical efficacy and (iii) without recommendations or guidelines regarding the NIBS parameters to use (e.g., stimulation area, frequency, intensity, polarity, duration, as monotherapy or coupled with cognitive training, etc.), (iv) taking into consideration the huge amount of time and energy that researchers, patients and caregivers have to invest in this kind of experimental protocols. Current published reviews and meta-analyses, however, provide conflicting evidence and little information on the real utility of NIBS for aphasia, all concluding that more multicenter RCTs, with larger populations and homogenous intervention protocols are required.

Critically, all previously published meta-analyses evaluated NIBS effects immediately after treatment, but monitoring outcome over time after treatment is crucial in order to evaluate which treatment is really effective and which patients might benefit the most. NIBS longer-term results are very important in order to understand their efficacy and safety. In clinical practice, demonstrating a short-term effect of rehabilitation is an insufficient result; what matters is a long-term preservation of positive achievements. In contrast with previous systematic reviews on this topic, which analyzed stimulation effects immediately after treatment, the purpose of this meta-analysis was to systematically synthesize and compare NIBS long-term efficacy in language recovery, in order to verify whether there are new and valid alternatives to improve aphasia treatment, eventually by coupling SLT with rTMS or tDCS. Secondly, because previous

studies [43,52] revealed a greater positive outcome of rTMS compared to tDCS, we assessed whether the two NIBS effect sizes significantly differed from each other also at follow-up. Furthermore, immediate post-treatment effects were compared with those reported at follow-up to evaluate changes over time. By grouping and contrasting subsets of studies according to different methodological aspects, further sub-analyses investigated potential influences of the study design (such as analysis including only tDCS RCT studies) and the post-stroke interval: chronic (more than six months after stroke) vs subacute (less than six months after stroke). Finally, the online software GRADE Pro GDT was used to qualify the evidence (https://gradepro.org).

## 2. Methods

This systematic review was conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [54].

### 2.1. Literature search and study selection

Four electronic databases - MEDLINE (accessed by PubMed, https://www.ncbi. nlm.nih.gov/pubmed), PsycARTICLES (via EBSCOHost, https://search. ebscohost.com), PsycINFO (via EBSCOHost) and Web of Science (https://webofknowledge.com/) - were searched for studies investigating post-stroke aphasia treatment using either rTMS or tDCS stimulation, alone or combined with other therapies. The considered papers were published between August 2004 and February 2019.

Keywords were: (1) “tDCS”, “transcranial direct current stimulation”; “transcranial magnetic stimulation”, “TMS “ AND (2) “aphasia”, “language disorder”.

Studies were selected according to the following inclusion /exclusion criteria:

- **Inclusion criteria:**
  - interventions designed for adults with post-stroke aphasia,
  - rTMS or tDCS stimulation studies (alone or combined with other therapies),
  - rTMS or tDCS were specified as the main intervention/ treatment,
  - cephalic stimulation designs only (at least one electrode was positioned on the scalp, the reference electrode could be extra-cephalic, such as on a shoulder),

- minimum 4 weeks (1 month) of follow-up,
- at least four aphasic participants,
- peer-reviewed publications,
- only RCTs or crossover designs,
- published in English,
- when several articles derived from the same study, either with increased recruitment or extended follow-up evaluations, we chose the one with the higher number of participants and the most complete data reported at follow-up,

- **Exclusion criteria:**
  - interventions designed for other types of post-stroke disorders or aphasia not due to stroke,
  - other types of brain stimulations such as transcranial random noise stimulation, electroconvulsive therapy, etc.,
  - open-label studies, e.g. [55–57],
  - studies involving less than 3 stimulation sessions over the same cortical region per patient,
  - extra-cephalic stimulation sites, e.g.[58],
  - a short follow-up period (less than one month), e.g. [59],
  - case reports and research studies with less than four participants,
  - articles from the gray literature (i.e., literature that is not formally published in sources such as books or journal articles, e.g. unpublished Ph.D. thesis),
  - presentations from international meetings with no specific data provided, perspective and opinion publications, case reports, series of cases, previous reviews or meta-analyses,
  - studies not published in, or translated into English,
  - studies that did not provide adequate information to analyze treatment effects (i.e., when we could not extract useful quantitative data) and we got no reply from the authors.

The retrieved papers were appraised to exclude those that clearly did not satisfy the inclusion/ exclusion criteria as revealed by the title, keywords, abstract or full-text screening; for example, several studies included patients with primary progressive aphasia, had an open-label design [55–57,60], or had a short follow-up period (1-3 weeks). Duplicates were removed through hand search. Additionally, to

identify other relevant trials we checked the reference lists of the included studies and previous meta-analysis and relevant reviews. Uncertainties regarding some inclusion were solved by the authors through discussion.

**2.2 Data extraction**

For each included paper, the relevant information to be extracted regarded:

i) the patients' characteristics: the sample size (treatment and control group), gender, age, time since stroke (chronic/ subacute), handedness, dropouts (Table 1);

ii) disorders' characteristics: lesion area, lesion type, aphasia diagnosis and instruments used for evaluation of the disorder, aphasia severity, outcome evaluation (Table 2);

iii) rTMS stimulation protocol: target area(s), rTMS frequency and intensity, number of pulses and duration, number of sessions, online or offline stimulation and associated therapy (if any), sham, adverse effects (Table 3);

iv) tDCS stimulation protocol: montage type (unipolar or bipolar, cathodic or anodic), electrode dimension, stimulation area, electrode position, stimulation hemisphere, reference electrode, current intensity, number of stimulations and duration, online vs offline stimulation and associated therapy (if any), sham, tDCS adverse effects (Table 4);

v) characteristics of the study: main objective, study design, language of the study, study arms, follow-up results and authors' conclusion, level of evidence on PEDro's scale (Table 5.1 & Table 5.2);

Means, standard deviations, sample size for experimental and control conditions were extracted. Across studies, aphasia assessment and outcome measures were heterogeneous, but for the purpose of this meta-analysis, only continuous aphasia measurements were chosen, namely, the primary outcome was based on picture naming accuracy or, if not reported, the explicitly declared primary outcome (e.g., aphasia battery results, reaction times, speech content units). When adequate information was not provided in the results description, means and standard deviations or standard errors were extracted from published figures using WebPlotDigitizer (https://automeris.io/WebPlotDigitizer/). Data analysis, standardized mean difference (SMD), sampling variance and summary analyses were computed for each included

study, using the "*metafor package*" for R (version 3.4.3) [61]. Hedges' ***g*** (computed as the difference between the mean of the experimental condition and the mean of the control condition, divided by the pooled standard deviation) was chosen for the effect size, instead of C*ohen's* ***d***, because due to low sample sizes across most of the studies, we considered it more adequate for our analysis: indeed, many researches included only seven/twelve participants [62,63]. If only standard errors were reported, we converted them into standard deviations (SD) using the formula $SD = SE\sqrt{n}$; SE= standard errors, n= number of participants [62]; if this method of data extraction could not be applied, the missing information was requested from the corresponding author.

For each effect, we included moderator variables related to: i) stimulation type (rTMS or tDCS), ii) time points (after treatment or at follow-up), iii) study design (crossover or RCTs), iv) time from the symptom onset (chronic or subacute).

In order to avoid entering multiple data points from the same study into the meta-analysis, results from a single experiment were aggregated to obtain a single measure per experiment. If several time points or control conditions were reported (e.g., comparing cathodal and anodal stimulation, or different brain regions stimulation within the same patients), data were extracted using the following criteria:

- from each study we chose one follow-up time point only, specifically, the one that represented the longest follow-up period matching the follow-up time points reported by the other studies included in the meta-analysis;
- only data regarding treatment effects on language recovery were extracted (e.g., aphasia battery scores, speech, etc.); fMRI data, blood flow or other parameters used as indicators of treatment effects were excluded;
- from each study, since often different stimulation protocols were tested, we chose one type only (e.g. montage, stimulation intensity), namely, the one that the authors considered as potentially effective, or, in the absence of such information, the type most frequently applied in the literature. This was done in order to reduce variability among the included studies;
- based on previous meta-analyses, and in order to reduce variability among studies, the preferred outcome was naming accuracy; in the absence of this measure we used a different outcome, e.g., the total score from the aphasia battery, speech content units, etc.;

- if a study reported different outcome measures for the same treatment (e.g., accuracy but also reaction times) we chose naming accuracy, the most frequently reported outcome in the included studies.

**2.3 Study Quality Assessment**

Methodological quality of the included studies was assessed using the Physiotherapy Evidence Database (PEDro) tool and a grade for the level of evidence was assigned to each study according to the modified Sackett Scale (Tables 5.1 and 5.2 for the level of evidence) [64,65].

PEDro is an eleven *yes/no* item scale (see Table 6.1 and 6.2) assessing the quality of clinical trials, which is considered a valid and comprehensive instrument previously applied in systematic reviews [66]. Items can be scored as either present (1) or absent (0) and the total score is obtained by summation, with higher values indicating greater quality: 9–10: excellent; 6–8: very good; 4–5: good; <4: poor [67].

The Sackett Scale includes five levels of evidence: Level 1 comprises high quality RCTs (PEDro ≥6) and meta-analysis, being divided into level 1a and level 1b, based on the number of RCTs. Level 2 evidence is also derived from RCTs but with a PEDro score < 6. Level 3 evidence refers to non-randomized clinical trials and case controls designs (retrospective studies comparing conditions including historical controls). Level 4 and 5 refer to case series, uncontrolled pre- post-treatment tests, observational studies, and case report designs.

Overall evidence was qualified using the grading of recommendations, assessment, development and evaluations (GRADEpro GDT, https://gradepro.org) and the Meader et al.'s [68] GRADE assessment checklist. GRADE provides a transparent approach and guidance on rating the overall quality of research evidence indicating four levels of evidence along a continuum (high, moderate, low, and very low) based on five factors: 1. risk of bias, 2. inconsistency, 3. indirectness, 4. imprecision, 5. publication bias. The risk of bias for each included study was evaluated using the simplified GRADE checklist proposed by Meader et al.[68], based on the Cochrane risk of bias tool items (Table 7.1 and 7.2).

For each meta-analysis pool effect, the level of heterogeneity, by means of the Q and $I^2$ statistics was calculated [69]. Q estimates the amount of variation due to sampling error, while $I^2$ evaluates which proportion of the observed variance reflects a real difference in effect sizes ($I^2$ values of 25%, 50%,

and 75% have been interpreted as representing small, moderate and high levels of heterogeneity, respectively). Influential cases were identified using the "*inf*" function from the "*metafor package*" for R [70–72].

Meta-analysis publication bias may be due to many factors like the fact that we explicitly included only peer-reviewed, English-written papers or that studies with stronger effects sizes are more likely to be published. Publication bias was assessed using the funnel plot tool together with the Egger's regression test [73] and the rank correlation test [74]. The trim and fill method (which imputes "missing" studies to create a more symmetrical funnel plot) [75] was used for bias correction only if the previously mentioned tests were significant, since a p value $< 0.05$ is consistent with a non-symmetrical funnel plot.

## 3. Results

The literature search initially retrieved 2497 publications and, following application of the eligibility criteria and duplicates removal, 141 studies were selected for a full text review; in the end, sixteen studies met the inclusion criteria. Figure 1 summarizes the inclusion process.

**[Insert Figure 1]**

### 3.1 Studies characteristics

Eight studies used tDCS as a therapeutic application for aphasia treatment: four randomized controlled trials (RCT) [76–79], three randomized crossover studies [80–82], one partial randomized crossover study [83] (Table 5.2). Eight studies investigated the effects of rTMS on aphasic patients after stroke: seven were RCTs [55,84–90] and one was a randomized partial crossover [91] (Table 5.1). The majority of these studies used a combined therapy, namely noninvasive brain stimulation was associated with language training online (behavioral treatment during the stimulation) or offline (taking advantage of the stimulation after effects, the linguistic training was delivered after neurostimulation); only two rTMS studies, [85,91], used neurostimulation as a monotherapy.

The methodological quality of the eleven RCTs, according to the modified Sackett Scale, was good, scoring between 6 and 10 on the PEDro scale (level 1b evidence). Four studies had randomized crossover

designs, while one had a partial crossover design [83] and their scores ranged between 4 and 9 (evidence level 1b and 2). The main risk of bias was the lack of allocation concealment and the carry over effect due to a very short washout period before the groups were switched to the other experimental arm; for instance, in the Fiori et al. [80] study, the intersession interval (between treatment and sham) was of only 6 days. Overall, the level of evidence ranged from good (level 2 – 4 studies) to very good (level 1b – 12 studies).

**3.2 Participants' characteristics**

The review included twenty studies involving 439 stroke patients diagnosed with aphasia (208 in the experimental condition, 202 in the sham condition and 29 in both experimental arms as part of crossover designs); 217 received rTMS stimulation (118 real rTMS and 99 sham) and 222 participated in tDCS experiments (90 real tDCS, 103 sham and 29 both conditions).

Participants' characteristics were heterogeneous among studies (Table 1), especially regarding:

- time interval from stroke – five papers focused on patients in a subacute stage (N= 184) ranging from 10 to 187 days post-stroke [76,78,84,86,87], while all the others included only participants with chronic aphasia (N= 255), the post-stroke interval ranging from 7 months to 9 years;
- aphasia diagnosis – this was obtained by means of different tests and aphasia batteries based on different approaches (neurolinguistics vs. psycholinguistics), the most frequent ones being: the Boston Diagnostic Aphasia Examination (BDAE), the Boston Naming Test (BNT), Psycholinguistic Assessment of Language Processing in Aphasia (PALPA), Aachen Aphasia Test (AAT), Aphasia Severity Rating Scale (ASRS) and the Western Aphasia Battery (WAB); then studies explicitly selected participants with non-fluent aphasia while 6 studies included all types of aphasia (Table 2);
- participants' age ranged between 37 and 77 years (Table 1),
- lesion – only left hemisphere stroke patients were selected but only general information about lesion site, extension, etiology were provided, with the exception of a few cases for which more details were reported, including MRI scans [80].

**3.3 Intervention**

**3.3.1. Target area.** The target area was identified in different brain regions depending on the experimental hypothesis and the stimulation type.

All rTMS studies, with one exception - Khedr et al. [87] that stimulated both hemispheres, stimulated anterior language areas (pars triangularis or pars opercularis) on the contralesional (right) hemisphere. The most commonly targeted brain region in tDCS experiments was Broca's area, only in one paper [83] a personalized approach was used: based on pre-treatment tDCS assessment sessions with different montages, the authors chose which area to target, namely anterior or posterior, contralesional or ipsilesional. Fridriksson et al. [79] chose the temporal lobe region with the highest naming related activation during fMRI, while Meinzer et al. (2016) tested the effectiveness of M1 (primary motor cortex) stimulation on language rehabilitation.

**3.3.2. Stimulation protocol: rTMS.** All of the included studies used an inhibitory stimulation protocol, with the exception of Khedr et al. [87] that applied a dual-hemisphere stimulation (excitatory, 20 Hz over Broca's area and inhibitory over the right, unaffected homologous of Broca's area), rTMS was delivered at an intensity between 110% and 80% of the resting motor threshold (7 out of 8 studies used a 90% RMT intensity) at a frequency of 1 Hz for a duration ranging between 10 minutes and 30 minutes for a total of 10/15 sessions (Table 3). Magnetic pulses were delivered with figure of eight shaped coils.

**Stimulation protocol: tDCS.** In all of the included studies, tDCS was unipolar and in general two equal sized electrodes were used; only Meinzer et al. [77] selected different dimensions: anode 5x7 cm, cathode 10x10 cm. Each electrode had an area of 25 $cm^2$ (5 cm×5 cm) or in some cases 35 $cm^2$ (5 cm×7cm), and with a few exceptions (that chose the best response area [79,83]) the anode was placed over the left, anterior language areas and the cathode over the right supraorbital region.

**3.3.3.** The **intensity and duration** of the stimulation were heterogeneous across studies, tDCS being delivered at an intensity of 1 mA or 2 mA (7 out of 8 publications used 1 mA, current density = 0.028) for 10/20 minutes. Another relevant variation concerned the number of sessions, that ranged between 5 [80,81] and 16 [77]. The follow-up period was very broad, varying from one/ two weeks up to 12 months, and some studies had many follow-up time points (e.g. Barwood et al. [85] evaluated the rTMS effects at 1 week, 2 months, 8 months and 12 months after stimulation), but in this meta-analysis only a period between one and six months was taken into consideration.

**3.3.4. Associated therapies.** In two rTMS studies [85,91] the treatment was limited to neurostimulation; in all other cases rTMS and tDCS were delivered together (during the stimulation or immediately after) with a broad range of aphasia classic therapies like: speech and language training for 30 – 60 minutes two-five times a week, picture-naming activity during every stimulation session, conversational therapy, word-finding therapy and computerized anomia treatment (Table 3 and 4).

**3.3.5. Placebo:** All the RCTs and randomized crossover studies, apart from Marangolo et al. [81] and Xue-yan Hu et al. [90] were double-blind sham-controlled, i.e., investigators and patients were blinded to the treatment allocations. Randomization was used to assign patients to the treatment or control group but the method of randomization was not always reported (Table 7.1 and 7.2). In the rTMS experiments, sham stimulation was obtained by positioning the angle of the coil at 90° perpendicular to the skull [86,87,91] or with a sham coil [84,85,88,89]. In the tDCS experiments, the sham condition implied turning off the stimulation after a very brief period, 15 - 60 seconds.

**3.3.6. Outcome measures.** Outcome assessment varied largely across studies and included: picture naming, naming reaction times, comprehension, fluency (discourse productivity), grammatical accuracy, lexical selection, general language scores on aphasia batteries (e.g., Western Aphasia Battery - Aphasia Quotient), single photon emission-computed tomography (SPECT) scans, relation between cerebral blood flow (CBF) and language recovery etc.

**3.3.7. Adverse Effects.** Overall, both rTMS and tDCS were well tolerated and only common, mild side effects, such as local discomfort at the stimulation site (itching, tingling) or dull headache and dizziness [79], were registered. Importantly no study reported significant differences between the active and the control group regarding unpleasant effects, but unfortunately almost half of the included papers did not provide such information [80–82].

**[Insert: Table 1, Table 2, Table 3, Table 4, Table 5.1 & Table 5.2, Table 6.1 and 6.2, Table 7.1 and 7.2]**

### 3.4. Meta-analysis results

Hedges' ***g***, a measure of effect size, was computed for each study and pooled into the meta-analysis in an effort to obtain a better understanding of how well the post-stroke aphasia NIBS treatment worked (the primary outcome was based on picture naming accuracy). Hedges'***g*** interpretation is very similar to Cohens'd (a ***g*** of 1 indicates that the two groups differ by one standard deviation, a ***g*** of 2 indicates they differ by two standard deviations). Cohen suggested a rule of thumb for interpreting the results: small effect = 0.2, medium effect = 0.5 and large effect = 0.8 [62].

In order to calculate the treatment effect, the standardized mean differences (SMD) were pooled using the **random-effects model** regardless of the heterogeneity test results (Q or $I^2$), since there is a certain amount of variance between studies due to their particular characteristics (e.g., stimulation parameters, associated therapies, patients' characteristics). Table 8 contains the test results from all the analyses.

**[Insert Table 8]**

**3.4.1. rTMS vs. tDCS follow-up efficacy** was the main question of the present study; the meta-analysis of 11 RCTs and 5 crossover studies showed a significant medium effect of noninvasive brain stimulation for post-stroke aphasia rehabilitation (overall SMD of 0.53; 95% CI = [0.30, 0.75], p <.0001; $I^2$ =24.78%), see Figure 2. When separately investigating the effects of rTMS and tDCS, though, both techniques produced a statistically significant effect: an rTMS pooled analysis revealed a moderate effect size (rTMS: SMD = 0.71; 95% CI = [0.43, 1.00], p <0.0001; $I^2$ =3.54%; N= 8), while tDCS produced a significant but small effect size (tDCS: SMD= 0.33; 95% CI = [0.03, 0.62], p =0.02; $I^2$ =18.32%; N= 8); nevertheless the Test of Moderators, comparing the two techniques did not reveal a statistical significant difference between the two (QM(1) = 3.376, p = 0.066). Since these data are mainly based on naming scores (2 studies used *speech* as the main outcome [82,91] and 1 study [83] used the *WAB-QB scores)* the effect of NIBS on language will be more appropriately referred to as the effect on naming.

**[Insert Figure 2]**

Although Q-statistic and $I^2$ tests provide evidence for heterogeneity, they do not offer an indication about which studies may disproportionately influence heterogeneity. Baujat et al. [92] proposed a plot to reveal those papers which contribute more heavily to heterogeneity and overall outcome (Figure 2.1.0). Studies in the top right quadrant of Figure 2.1.2 for tDCS [78] and Figure 2.1.1 for rTMS [88] were those with the higher contribution to overall heterogeneity and final results. Nevertheless, the visual inspection of a plot might not be conclusive; therefore, to identify potential outliers and influential studies, Viechtbauer and Cheung [93] proposed an influential test derived from standard linear regression. Results indicated that Tsai et al. [88] (study 6 on the Baujat plot), for the rTMS subgroup, and Spielmann et al. [78] (study 7 on the Baujat plot), for the tDCS subgroup, yield observed effects that were well separated from the rest of the data. Looking at the forest plot it can be easily seen that Tsai et al. [83]'s paper crucially contributes to the final result (weights = 10.61%) and Spielmann et al. [78]'s study can be considered an outlier since the reported effect size is negative (-0.18), contrary to all the other studies: indeed, in this study tDCS on subacute patients seems to have a slightly (not statistically significant) negative effect on language recovery.

**[Insert: Figure 2.1.0, Figure 2.1.1, Figure 2.1.2]**

**Publication Bias:** The funnel plot for rTMS, tDCS and the overall publication bias (Figure 220, 2.2.1 and 2.2.2) was considered symmetrical given the fact that neither the Rank Correlation nor Egger's Regression Test were statistically significant (Table 8); so, the conclusions regarding the rTMS and tDCS follow-up efficacy, taken alone and pooled together, remained unchanged.

**[Insert: Figure 2.2.0, Figure 2.2.1, Figure 2.2.2]**

**3.4.2. Only tDCS RCTs** were then analyzed separately (N=4) in order to exclude possible confounding factors like the carry over effects, which were present in the majority of the crossover trials [80–83]. The "*only RCTs analysis*" was not conducted on the TMS studies because, the only TMS randomized crossover trial was the one by Medina et al. [91] who provide the follow-up results for treatment and control before the sham participants crossed over into the real treatment group, which means that we extract the same data as from an RCT study.

The overall weighted mean effect size for rTMS and tDCS was 0.49 (p =.0001; 95% CI: [0.24, 0.75]; N=12). The test for heterogeneity was not significant (Q= 15.57, p=.16, $I^2$= 33.14%), indicating that the variance between studies was not larger than expected when including random sample error (Figure 3). Taken separately the tDCS RCTs effect size was small and non-significant SMD = 0.20 (p = 0.29; 95% CI: [-0.15 - 0.51]; N=4), and as expected the Test of Moderators showed that the difference between the TMS RCTs and tDCS RCTs estimates was statistical significant (QM (1) = 5.61, p = 0.018).

**[Insert Figure 3]**

The Baujat plot (Figure 3.1.0, 3.1.2) and the Viechtbauer and Cheung [93] influential test identified two studies as potential outliers: Spielmann et al. [78] and Fridriksson et al.[79] (study 3 and study 4) for the tDCS subgroup. The **publication bias** tests were not significant and the funnel plots (Figure 3.2.0, 3.2.2) can be considered symmetrical.

**[Insert: Figure 3.1.0, Figure 3.1.2, Figure 3.2.0, Figure 3.2.2]**

**3.4.3. After vs. Follow-up:** Our meta-analysis focus was the NIBS follow-up efficacy but we also collected and analyzed the SMD immediately after treatment in order explore the effect of time on brain stimulation efficacy (once again, the primary outcome was based on naming scores). Separate analysis of tDCS and rTMS publications immediately after treatment (no more than one week later) revealed a statistically significant but small SMD of 0.34 (95% CI = [0.023, 0.65]; p = 0.035; N=8) for tDCS, while for rTMS studies, the SMD of 0.66 (95% CI = [0.37, 0.94]; p <.0001; N= 7) can be considered medium (Figure 4). Furthermore, the paired t-Test comparing before vs after effect sizes for each technique yielded no significant difference between the two time points, indicating that the effect size observed in the **rTMS** (t (6)= -0.54, p = 0.24; 99%CI =[ -0.54 , 0.24]) and **tDCS** (t (7)= 0.14, p = 0.88; 99%CI = [-0.16 , 0.17]) studies immediately after treatment did not change significantly when measured at follow-up (an interval extending from one to six months after the last stimulation session).

**[Insert Figure 4]**

The Viechtbauer and Cheung [93] influential test as the Baujat plot (Figure 4.1.0, 4.1.1, 4.1.2) showed no potential outliers for the rTMS alone, while the Spielmann et al. [78]'s and Marangolo et al. [82]'s experiments were identified as potential outliers for tDCS effects. The tests for **publication bias** indicated no need for bias correction (Figure 4.2.0, 4.2.1, 4.2.2).

**[Insert: Figure 4.1.0, Figure 4.1.1, Figure 4.1.2, Figure 4.2.0, Figure 4.2.1, Figure 4.2.2]**

**3.4.4 Chronic vs. Subacute:** The stroke phase (subacute or chronic) determines the brain state and ongoing plastic changes which influence treatment effects. To investigate possible differences in NIBS efficacy at follow-up taking into consideration the time passed from the stroke event, studies including only chronic patients (N=11, tDCS=6 and rTMS=5) were analyzed separately from those with subacute aphasic participants (N=5, rTMS=3, tDCS=2) and the two techniques were compared for each subgroup.

This choice was made based on the previous analysis (rTMS vs. tDCS at follow-up) showing that rTMS and tDCS produced different results especially concerning the subacute population.

**rTMS vs. tDCS in chronic aphasia (more than six months after the stroke):** The outcome revealed a significant weighted mean effect sizes of 0.62 (95% CI: [0.25, 0.98], p=0.001, N=5) for the rTMS studies and 0.54 (95% CI: [0.20, 0.86], p = 0.001, N=6) for the tDCS studies, while the Test of Moderators (QM (1) = 0.20, p = 0.65) showed no significant difference between the two effect sizes (for details see Figure 5, and funnel plots figures 5.2.0, 5.2.1, 5.2.2).

[**Insert Figure 5**]

Taking a close look to the influential studies, the test revealed three potential outliers: Wang et al.[89] and Tsai et al.[88] for the rTMS subgroup, and Fridriksson et al. [79] for the tDCS subgroup (Baujat plot figures: 5.1.0, 5.1.1, 5.1.2).

[**Figure 5.1.0, Figure 5.1.1, Figure 5.1.2, Figure 5.2.0, Figure 5.2.1, Figure 5.2.2**]

**rTMS vs. tDCS in subacute aphasia (less than six months after stroke):** The number of studies investigating the effects of NIBS exclusively on a subacute population was particularly small (rTMS=3 and tDCS=2) The pooled analysis revealed a statistically large and significant SMD of 0.85 (95% CI = [0.30, 1.32]; p = 0.0004) for rTMS studies in subacute patients, while for tDCS the SMD was not calculated because, with such a small number of studies, the result is neither solid nor reliable.(Figures 6, 6.1.0., 6.1.1, 6.2.0, 6.2.1).

[**Insert Figure 6**]

[**Insert: Figure 6.1.0, Figure 6.1.1, Figure 6.2.0, Figure 6.2.1**]

### 3.5. GRADE assessment

Overall evidence was qualified using GRADE (for RCTs and crossover). Low quality of evidence (i.e., the true effect might be markedly different from the estimated effect) shows that people with post-stroke aphasia may have a small to medium long-term benefit from tDCS treatment when compared to the control group; while a high quality of evidence (i.e., the authors believe that the true effect is probably close to the estimated effect) indicates that aphasic patients might have a medium to large benefit from rTMS treatment.

Given the fact that the online GRADEpro software offers only two options for the study designs, namely RCTs or observational studies, we chose RCTs, because the majority of the included studies were randomized designs. The level of evidence for RCTs was downgraded due to the carry over effect in the crossover designs but also for the lack of precision due to incongruent effect size direction and the large confidence intervals. The GRADE data are shown in Table 9.

[**Insert Table 9**]

## 4. Discussion

In recent years, an increasing number of studies investigated whether tDCS or TMS can promote aphasia recovery, in an attempt to potentiate the therapy-induced clinical benefits and/or to shorten the period of treatment.

As mentioned in the introduction, the aim of this comparative meta-analysis was to examine the long-term efficacy and reliability of NIBS (tDCS, rTMS) as an intervention for post-stroke aphasia. In other words, we aimed at assessing to what extent the therapeutic promises are confirmed in the long term, so

that rTMS and/or tDCS (either as an add-on therapy to SLT or as monotherapy) can be considered really effective.

The overall analysis, including 16 independent follow-up effect sizes (mainly based on naming scores), revealed a medium and significant effect of NIBS (rTMS and tDCS studies pooled together) compared to the control condition (sham or pre-treatment). These data are highly relevant for the rehabilitation research field, suggesting that rTMS and tDCS may improve aphasia recovery and produce durable results, especially for the naming performance. The effect size hereby found is comparable to those reported by other recent meta-analyses investigating the same topic, despite the fact that their analyses were based on data recorded immediately after the end of treatment [43,52]. Although the magnitude of the treatment effect size was larger in the rTMS than in the tDCS studies, this difference was not statistically significant. Nevertheless, when balancing these results by the GRADE level of evidence it seems that: i) while rTMS coupled with SLT can be considered effective (a medium effect size at follow up and a high level of evidence), ii) there are no consistent data to make a strong recommendation regarding the effectiveness of tDCS coupled with SLT in improving post-stroke aphasia (a small to medium effect size at follow up and a low level of evidence, as qualified with GRADE). This means that in some conditions (e.g., anodal stimulation in the subacute population), tDCS therapy could be less effective [78].

Critically, comparing the data immediately after treatment and at follow-up, we found no significant differences between the two time-points. Therefore, we can provide compelling evidence that the treatment effects are maintained in time, i.e., the changes observed at the end of the stimulation intervention remained roughly stable (they insignificantly decrease or do not improve) when measured again after a period extending from one to six months post-treatment.

Considering only RCT studies, in order to exclude eventual confounding variables, such as carry-over effects, we observed that the overall (rTMS and tDCS) effect size remained medium and statistically significant, but sub-analyses indicated an advantage of rTMS over tDCS. More precisely the tDCS RCTs effect size was small and not statistically significant. This result should be interpreted with caution since the number of studies is extremely small. From the four tDCS RCTs, two were conducted on subacute aphasics [76,78] and as previously observed, the tDCS effect seems to be sensitive to chronicity.

Furthermore, none of the tDCS RCTs, on chronic populations, stimulated the perilesional Broca's area; specifically, Meinzer et al. [77] applied anodal tDCS over the left primary motor cortex, while Fridriksson at al. [79] choose to stimulate the left temporal lobe, specifically, the region with the highest naming related activation during fMRI.

The sub-analysis by stroke chronicity confirmed the previous observations (based on data recorded immediately after treatment) [43], namely, that also at follow-up rTMS was effective in both chronic and subacute aphasic patients while tDCS was effective only in the chronic phase. Only two studies investigated the tDCS efficacy during the subacute phase [76,78] and both failed to find significant differences in language outcomes between groups (treatment vs sham). Based on the current literature data, it is unclear whether the difficulty to find an improvement (after tDCS stimulation in the subacute aphasic population) is because there is no effect at all or a "true effect" is too small to be detected with such a small number of studies. It has been speculated that an effect of tDCS might be difficult to achieve during the subacute phase, due to spontaneous recovery, that could mask the effects of rehabilitation interventions [76,78]. Another explanation might be the relation between the stimulation parameters (inhibitory vs. excitatory, ipsilateral vs. contralateral) and the dynamic mechanisms of post-stroke recovery (repair of damaged networks, activation of compensatory areas in the right hemisphere, or activation of previously functionally inactive pathways) and how well each one supports the other in order to enhance recovery. For example, Polanowska et al. [76] and Spielmann et al.[78] using anodal stimulation over the left Broca's area obtained a null effect, while You et al., [94] showed that auditory verbal comprehension improved significantly in subacute patients treated with cathodal tDCS over the right superior temporal gyrus, as compared to patients in the other groups (anodal tDCS applied to the left superior temporal gyrus and sham). In 2006, Saur et al. [95] reported that brain reorganization during language recovery might proceed in phases. Namely, they observed a reduced activation of the spared left language areas during the acute period, followed by the recruitment of the right language regions in the subacute phase, and a re-shift of peak activation to left-hemispheric language areas (which was associated with further language improvement) [96]. Considering this observation, and knowing that tDCS has a modulation effect (it only modulates those neurons that are potentially engaged in the execution of a given task) [28], it might be more appropriate to try to downregulate the right hemisphere during the subacute period (cathodal tDCS over the right language areas) and to activate

the perilesional regions during the chronic phase (eventually by using a bi-hemispheric stimulation: cathode over the right and anode over the left language areas). However, the choice of the stimulation type (inhibitory or excitatory) and the stimulation area (right or left hemisphere) depends also on the adopted recovery model (the "vicariation model" - right areas help recovery, the "interhemispheric competition model" - the right hemisphere excessively inhibits the left one, and the "bimodal balance-recovery model" - the quantity of spared neuronal structures determines the network reorganization) [38].

There are however several limitations in the present meta-analysis, as, for instance, the low number of studies (especially because many papers did not include a follow-up period), the risk of bias (present in the crossover designs) and the selection biases. The between-study heterogeneity and the risk of publication bias were low. Nevertheless, even if the funnel plot and the specific asymmetry tests did not indicate a significant publication bias, we restricted our search strategy to articles published in English, excluding potentially high-quality research data that were published in other languages or belonging to "gray literature". Crucially, all the comments and recommendations were based on publications reporting follow-up results; this means that other relevant information about efficacy, stimulation protocol and methodology might have been missed (for reviews see [40,42,43,49,52,53,97]). However, we believe that the relevant outcome is a permanent, or at least a long-lasting improvement, not just an immediate one. Another limitation is due to an important literature bias, namely, the lack of comprehensive aphasia assessment in patients receiving NIBS treatment. Since picture naming is one of the most frequently used tests for assessing improvement in language abilities after rTMS or tDCS [43], it was used as the main outcome for this review. We are aware that picture naming accuracy is not the unique measure of aphasia severity and, consequently, the meta-analysis results only reflect the effects of NIBS on naming in persons with aphasia.

Summing up, our findings add new data to the existing literature, by showing that, with the current stimulation procedures, the rTMS long-term effect size is moderate but more reliable independently of the patients' characteristics, while tDCS appears moderately effective for the chronic population. Importantly, study quality was lower in the tDCS subgroup (Table 9, GRADEpro evaluation). Many studies used crossover designs with a very small period between the sessions, therefore the final result (especially

at follow-up) was probably a mix between the different experimental conditions. Another important problem observed in tDCS studies was the lack of details regarding lesion size, and given the dimension of the tDCS electrodes (often 5x7 cm), it is not always obvious that all patients actually had a structurally intact cortex underneath the active electrode.

Based on the current data and the literature reviews (e.g. [27]), we can speculate that NIBS (tDCS and rTMS) are more effective on boosting the recovery process, not as a monotherapy (a treatment by itself), but rather as a complementary instrument coupled with SLT (only five included studies used rTMS and tDCS alone).

In conclusion, each technique has advantages and disadvantages: rTMS seems more effective but also more expensive and with a higher safety risk, while tDCS appears less effective but is user-friendly and could be applied at home with a relatively small cost. For these reasons, further evaluation of the utility of these methods for aphasia rehabilitation should combine efficacy and feasibility data, making a cost-benefit analysis possible. Still, in the future the most important challenge will be to collect clear evidence of the long-term efficacy in the everyday-life of these methods.

**Acknowledgments** This research was supported by the Center for Mind/Brain Sciences and University of Trento and by Ph.D. program sponsors: the Autonomous Province of Trento, the Fondazione Cassa di Risparmio di Trento e Rovereto and the Municipality of Trento.

We are grateful to all the authors that answered our e-mails and offered supplementary data from their studies.

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**Figure 1. Flow Diagram of study selection and inclusion.**

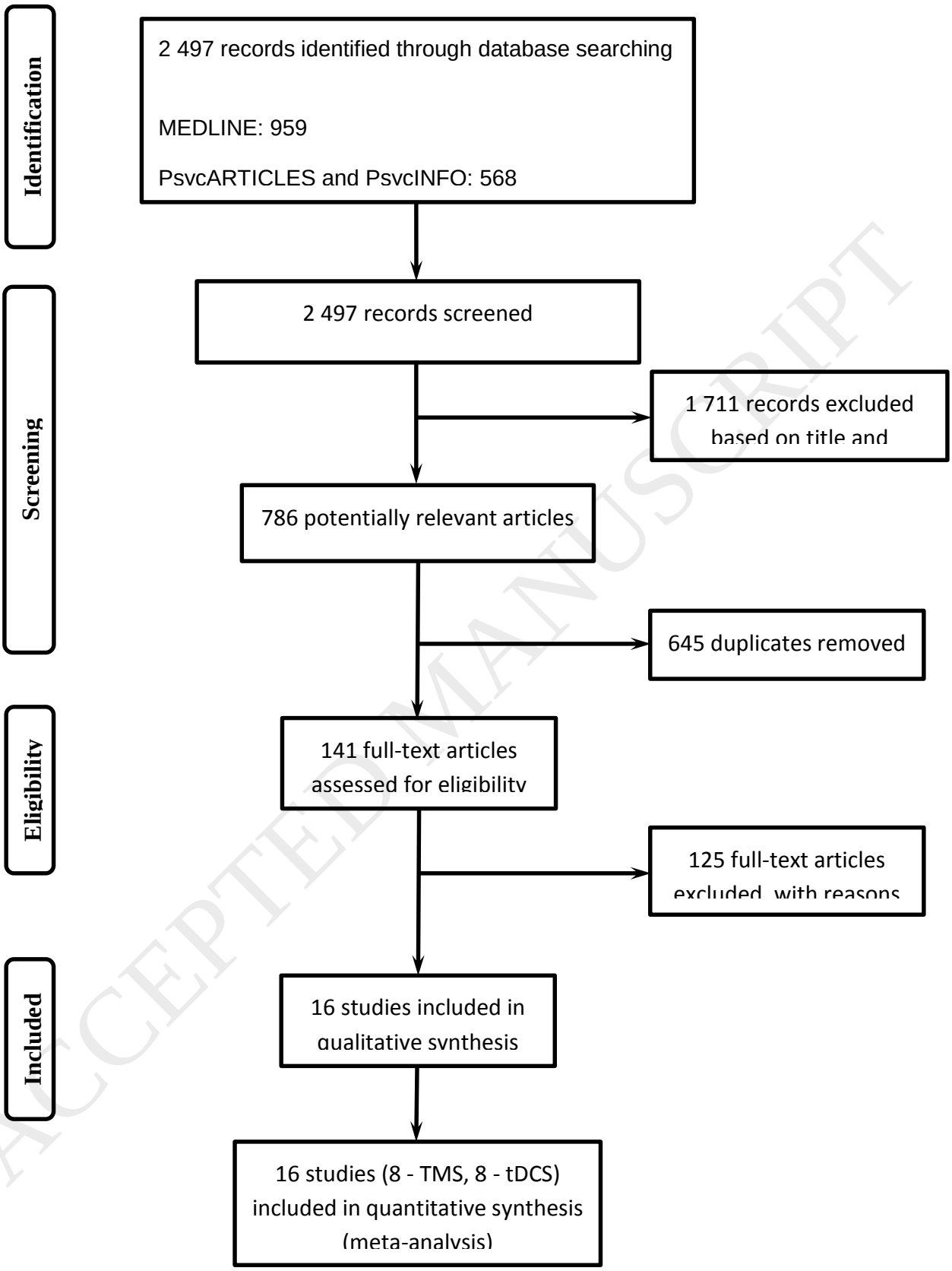

Figure 2: Forest plot of effect sizes, broken down by NIBS (TMS vs. tDCS), at follow-up

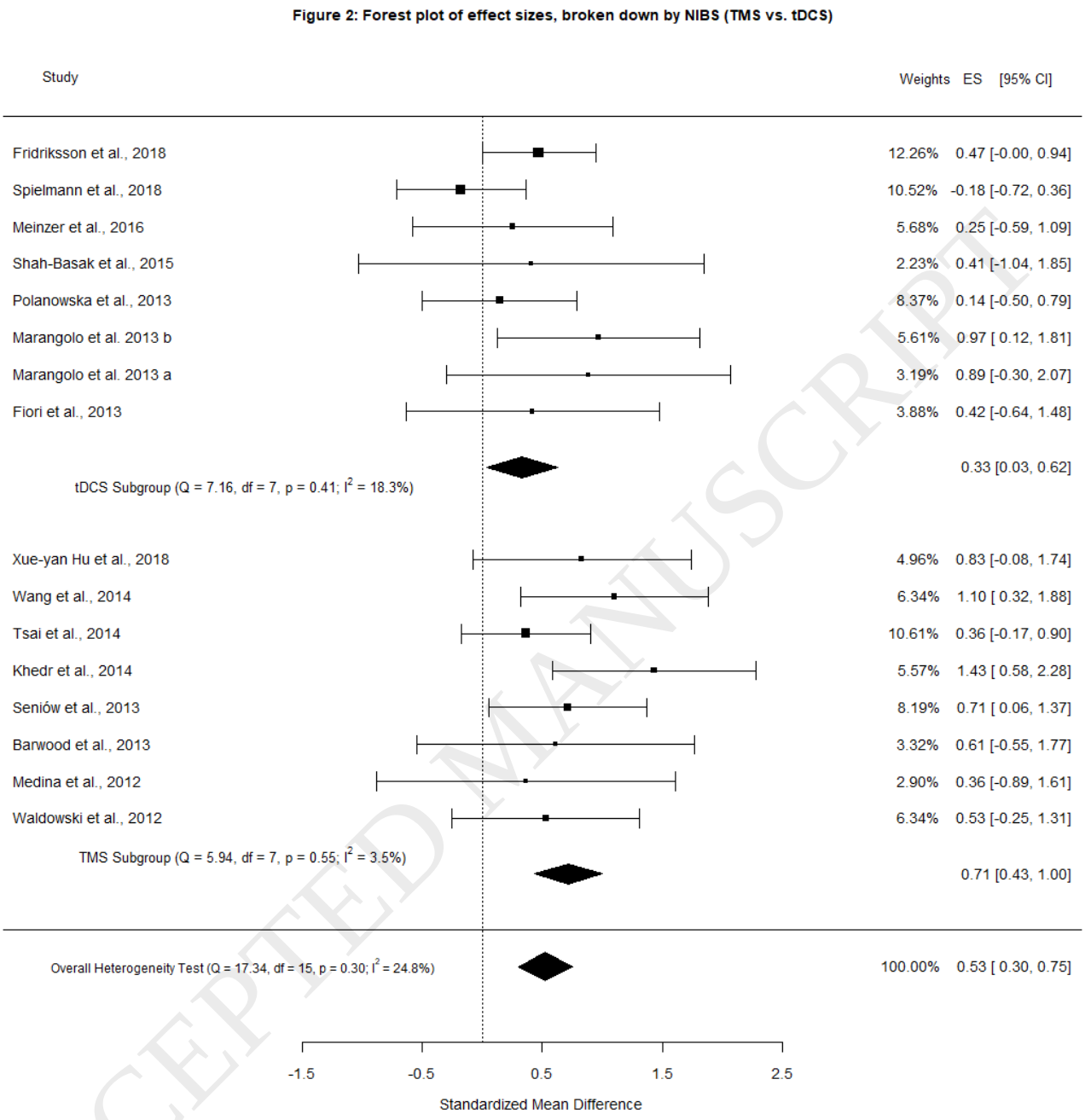

Figure 2.1.0: Baujat plot at follow-up (TMS & tDCS)

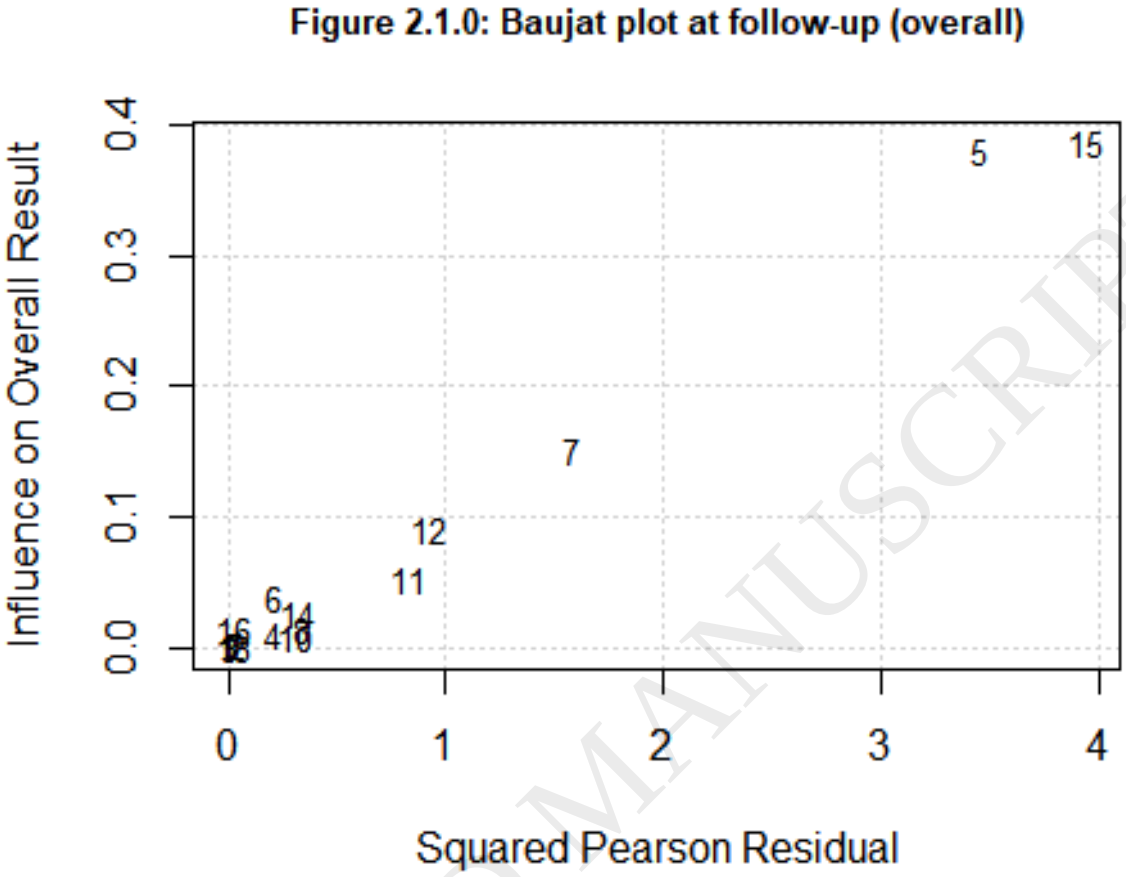


Figure 2.2.1: Baujat plot at follow-up (TMS only)

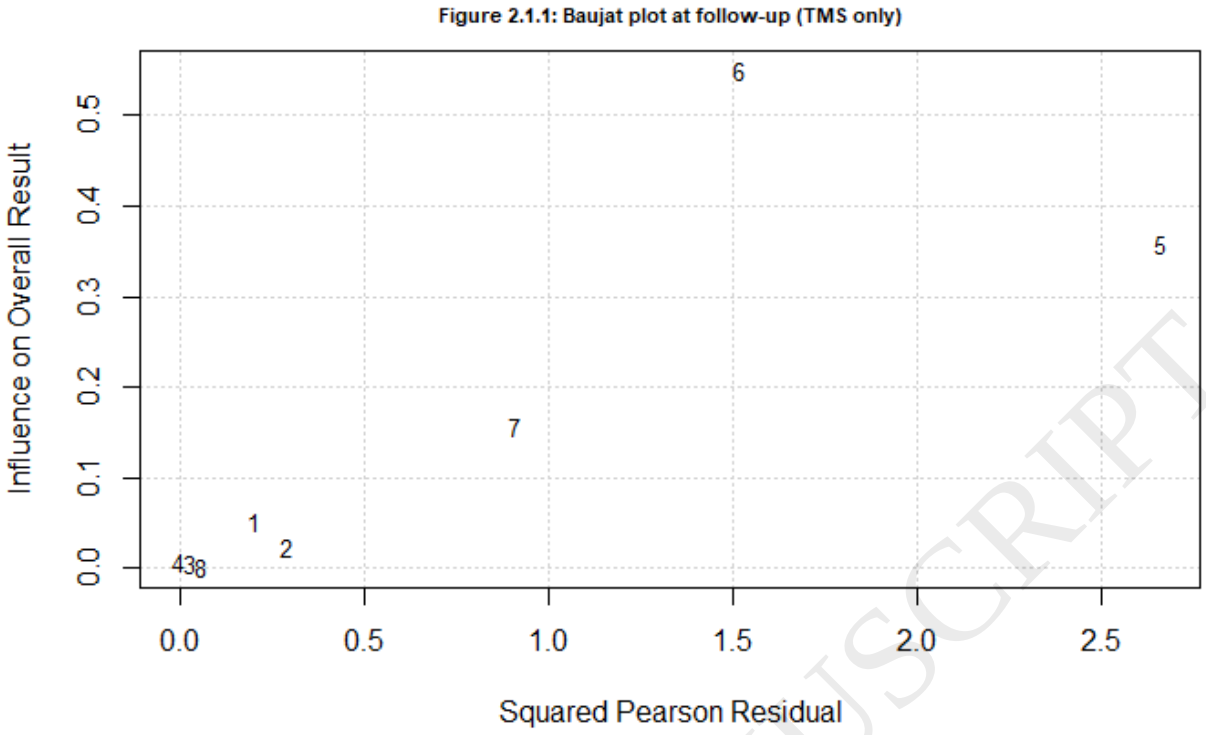


Figure 2.1.2: Baujat plot at follow-up (tDCS only)

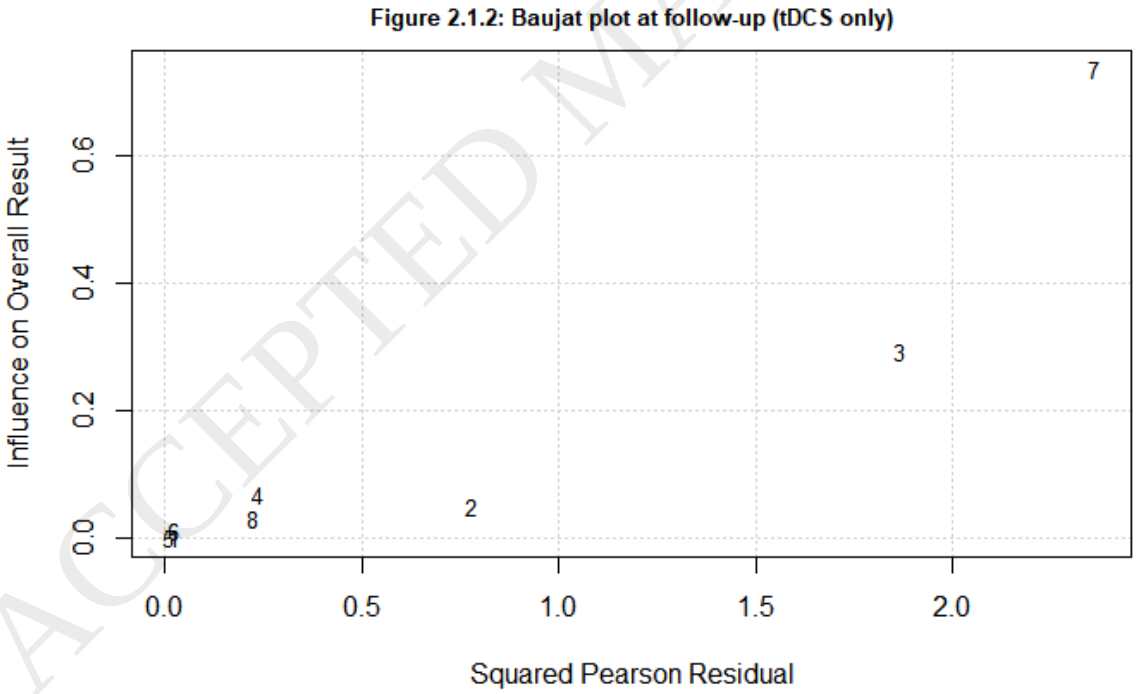


Figure 2.2.0: Publication bias assessed by the funnel plot at follow-up (TMS & tDCS)

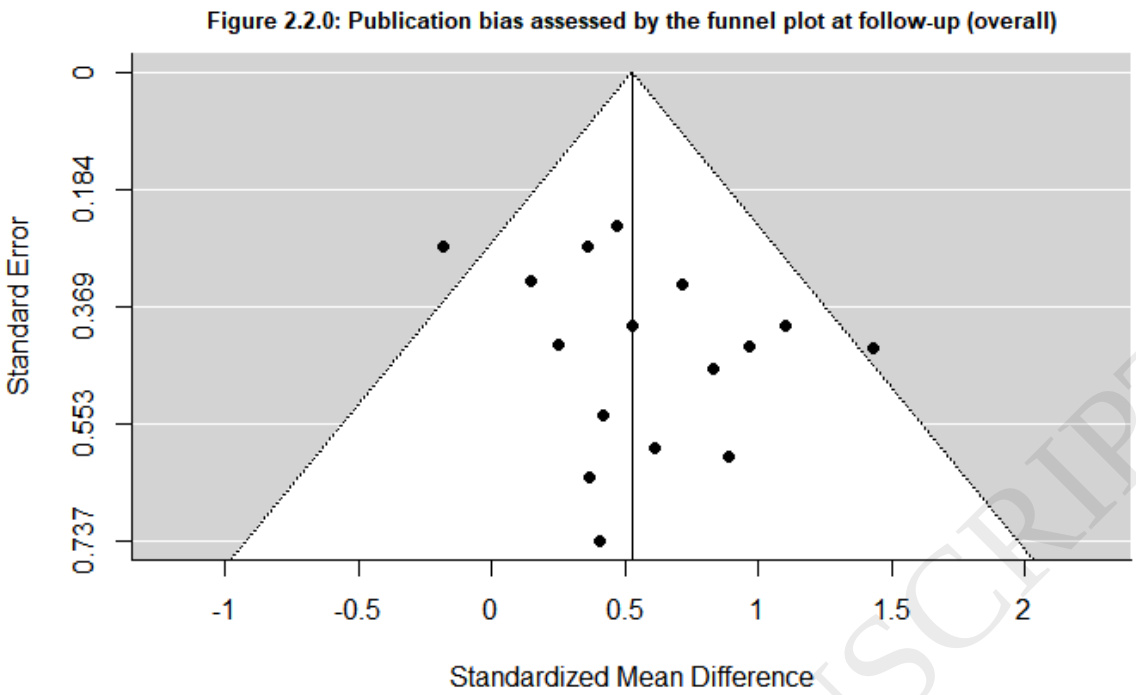


Figure 2.2.1: Publication bias assessed by trim and fill funnel plot at follow-up (TMS only)

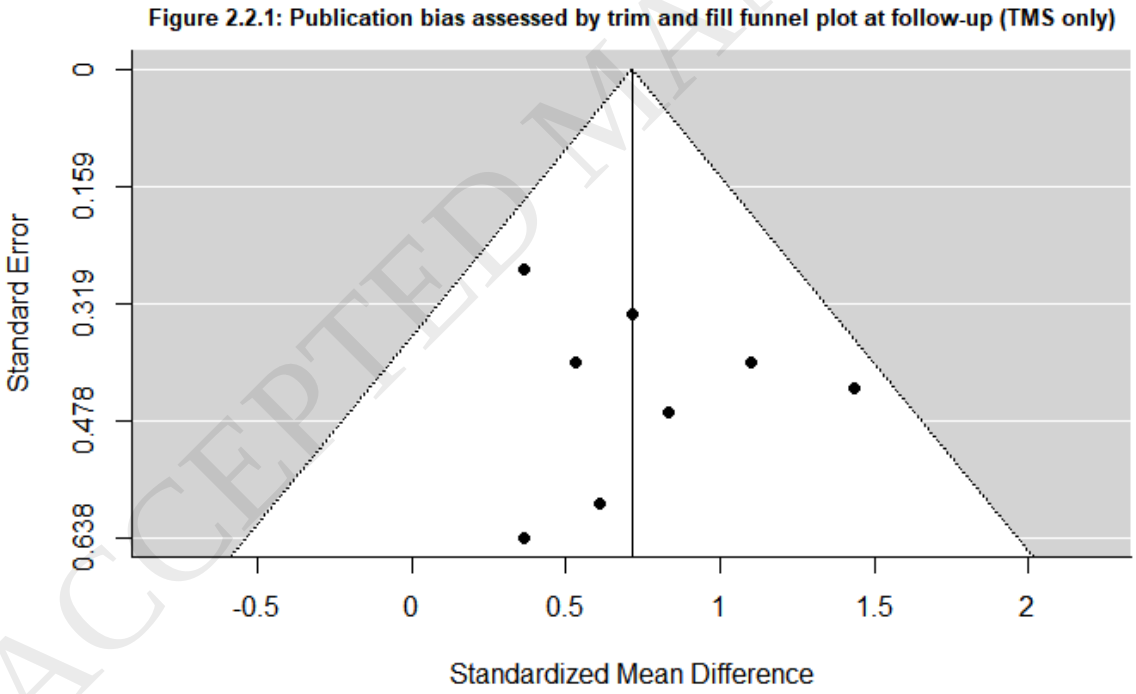


Figure 2.2.2: Publication bias at follow-up assessed by funnel plot (tDCS only)

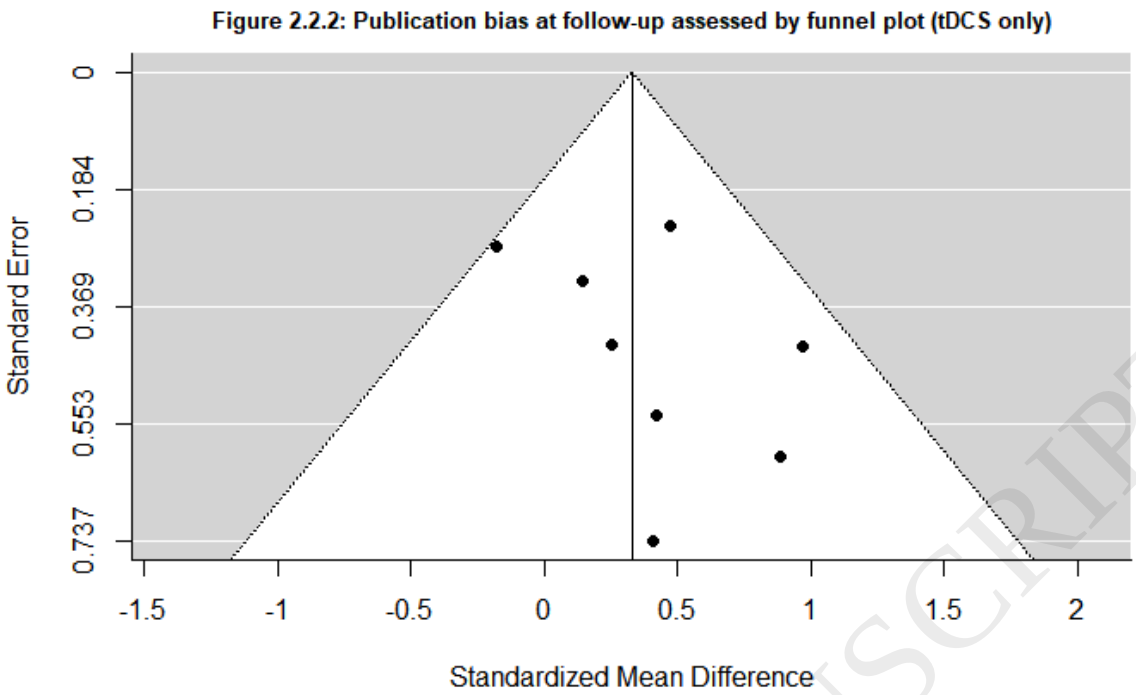


Figure 3: Forest plot of RCTs at follow-up, broken down by NIBS (TMS vs. tDCS)

**Figure 3: Forest plot of RCTs at follow-up, broken down by NIBS (TMS vs. tDCS)**

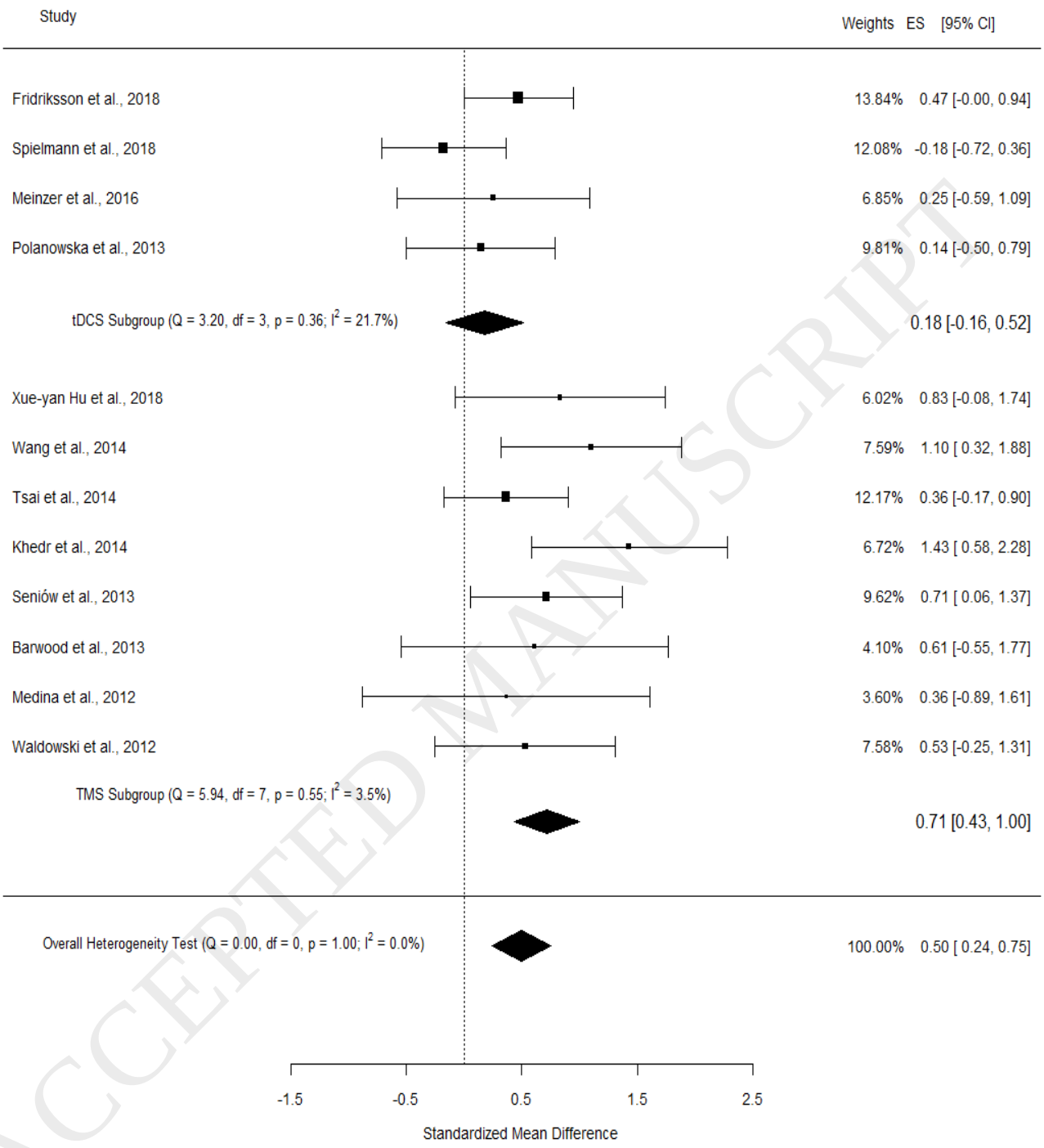


Figure 3.1.0: Baujat plot at follow-up only RCTs (TMS & tDCS)

**Figure 3.1.0: Baujat plot at follow-up only RCTs (overall)**

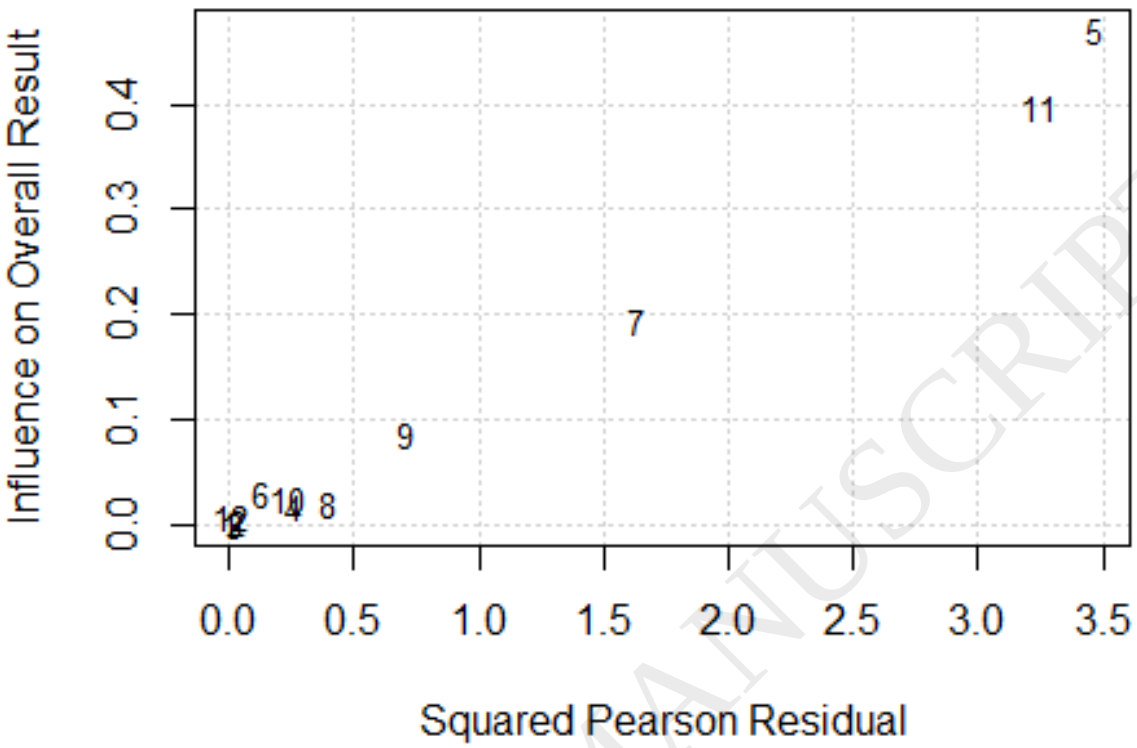


Figure 3.1.2: Baujat plot of tDCS RCTs at follow-up

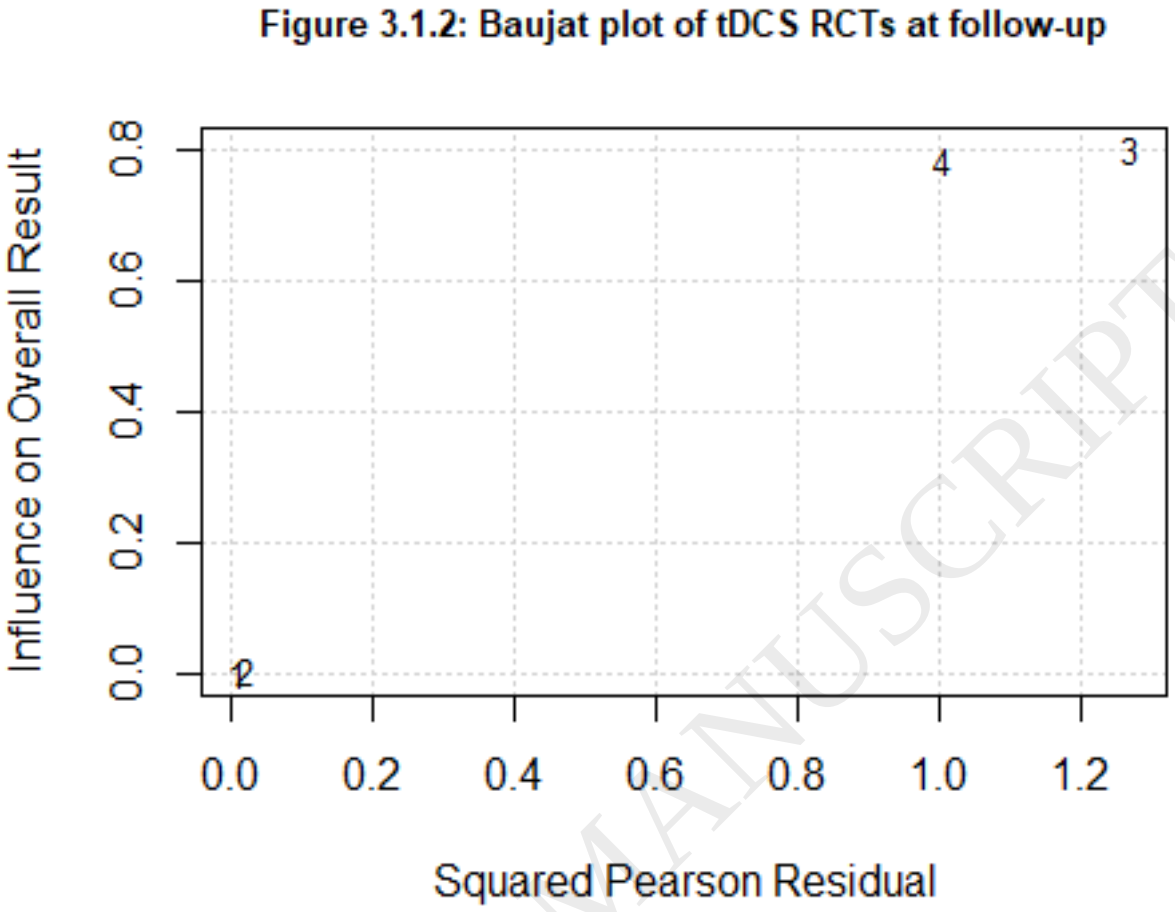


Figure 3.2.0: Trim and fill funnel plot at follow-up (overall RCTs)

**Figure 3.2.0: Trim and fill funnel plot at follow-up (overall RCTs)**

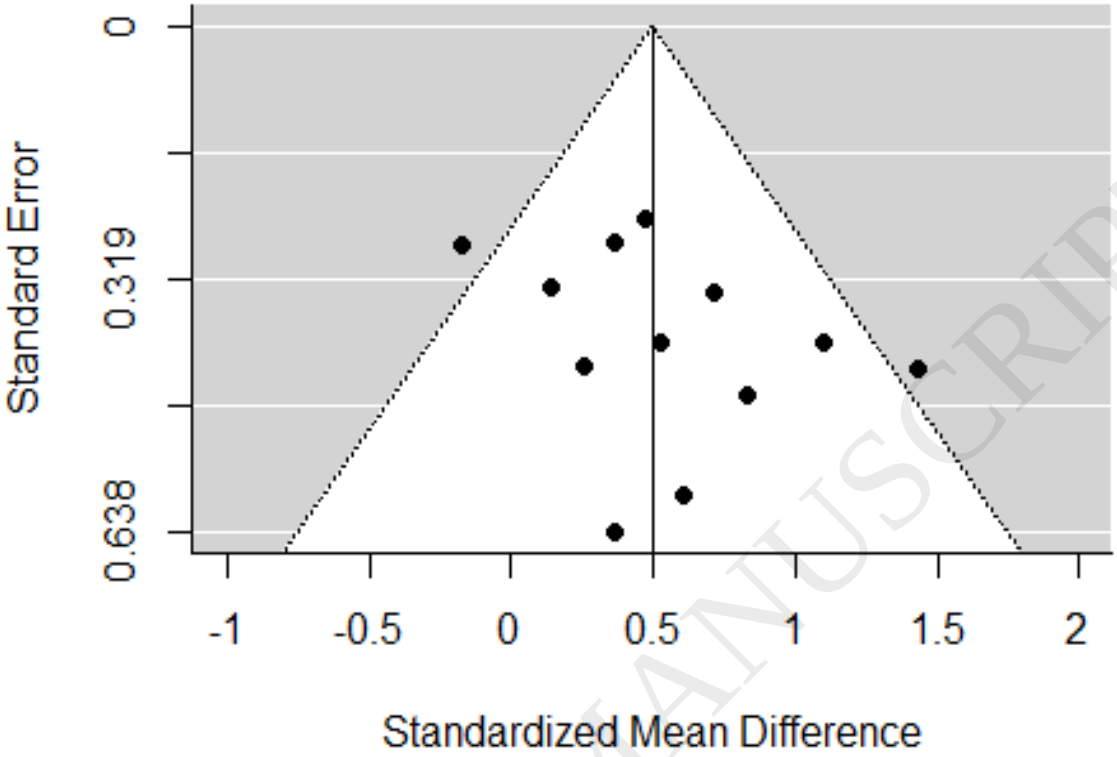


Figure 3.2.2: Trim and Fill Funnel plot of tDCS RCTs at follow-up

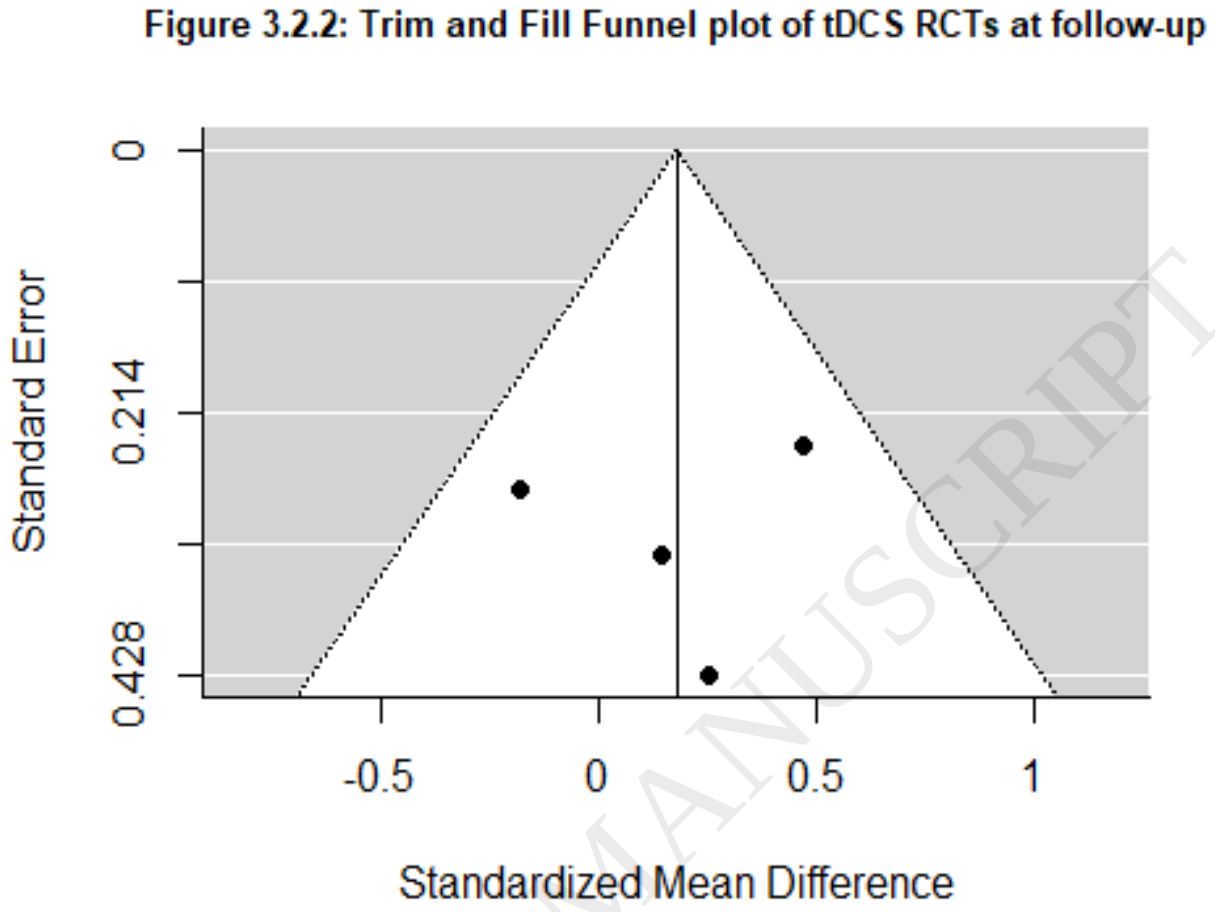


Figure 4: Forest plot of effect sizes immediately after treatment, broken down by NIBS (TMS vs. tDCS)

**Figure 4: Forest plot of effect sizes immediately after treatment, broken down by NIBS (TMS vs. tDCS)**

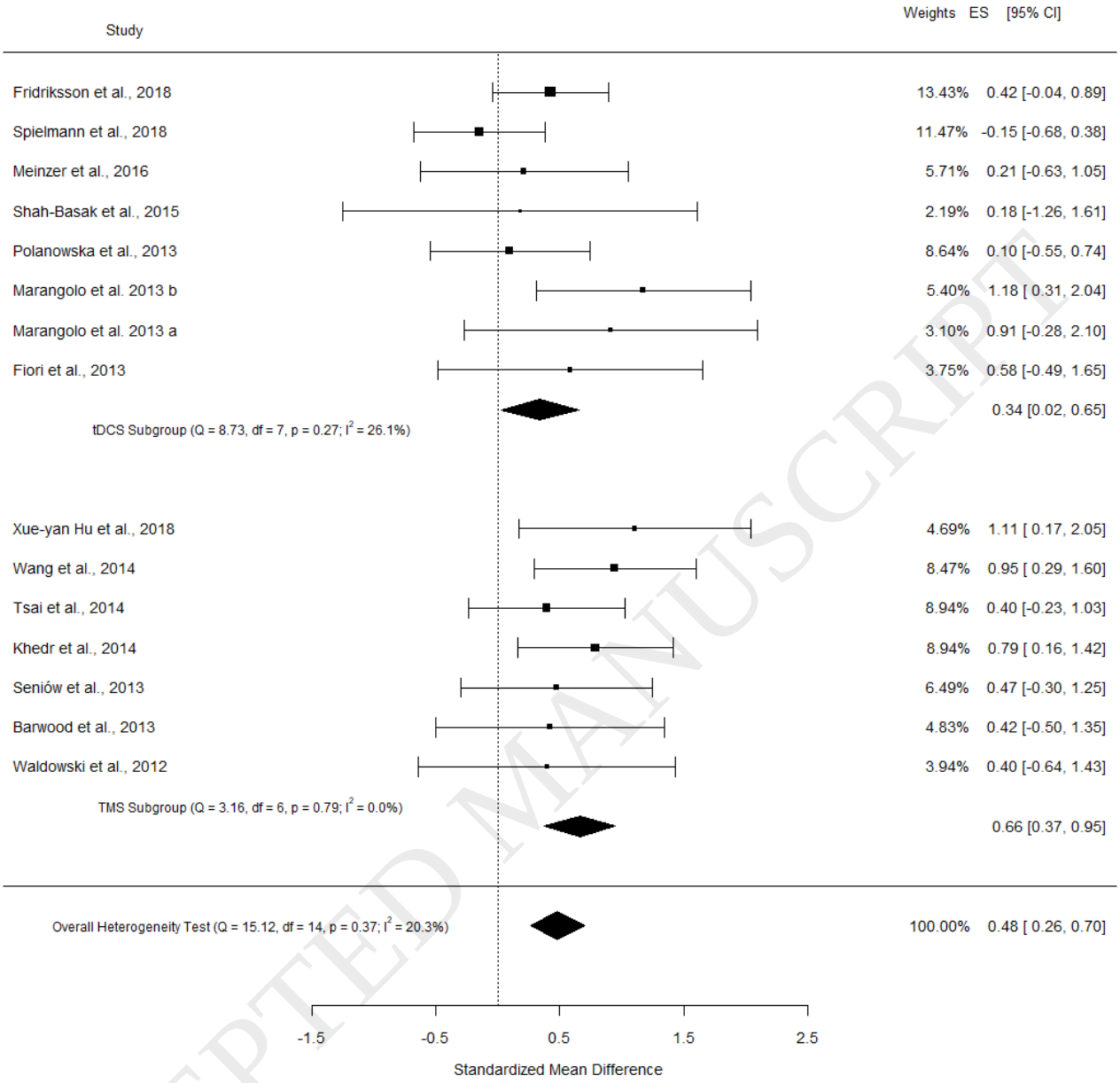


Figure 4.1.0: Baujat plot immediately after treatment (TMS & tDCS)

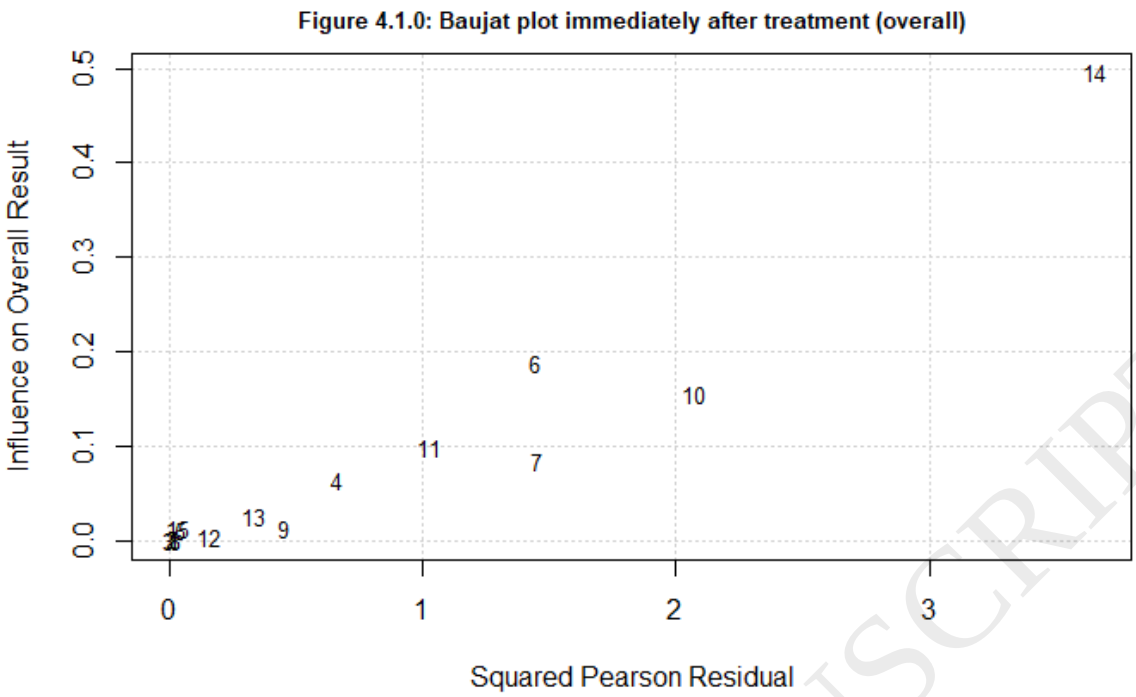


Figure 4.1.1: Baujat plot of TMS studies immediately after treatment

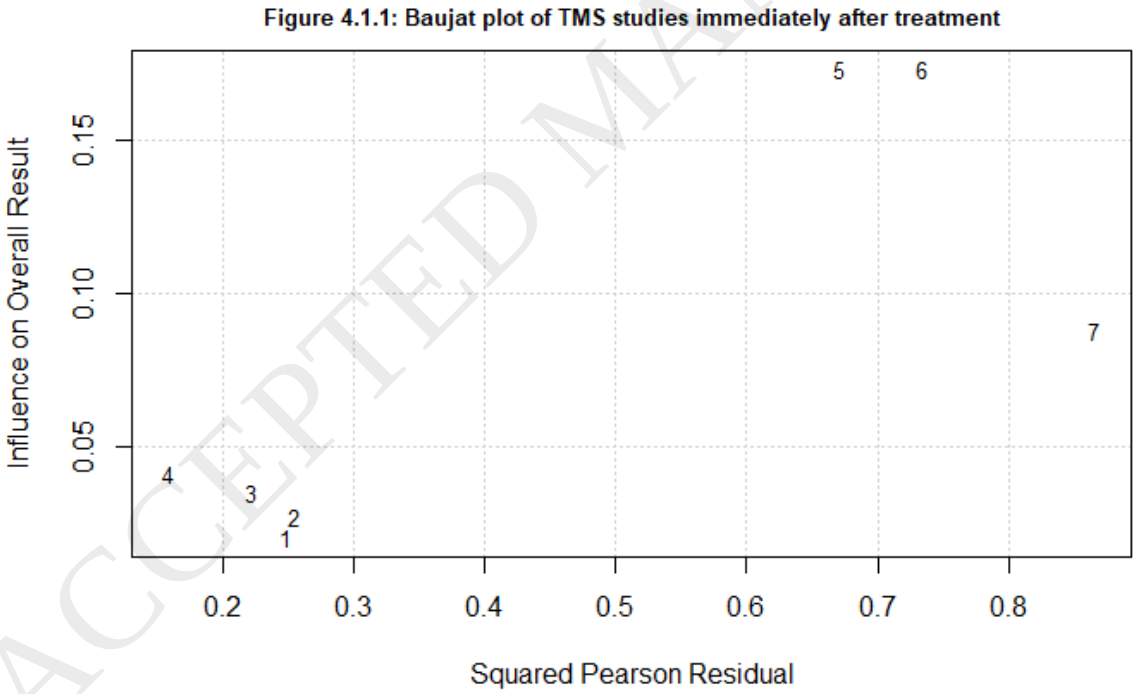


Figure 4.1.2: Baujat plot of tDCS studies immediately after treatment

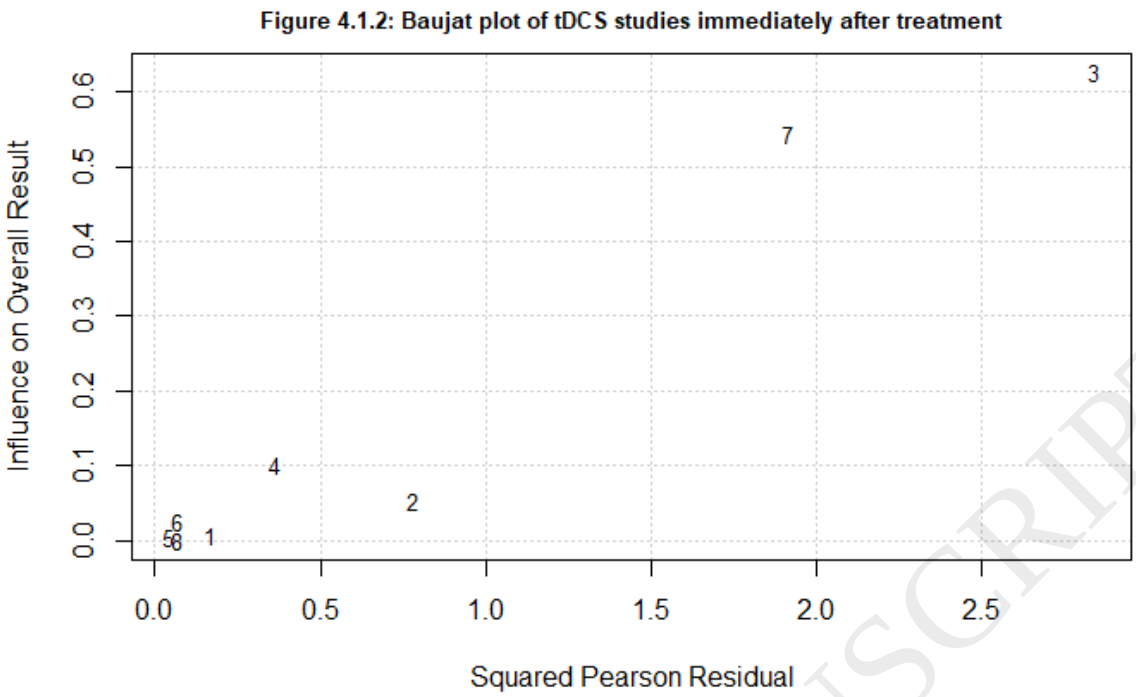


Figure 4.2.0: Funnel plot immediately after treatment (TMS & tDCS)

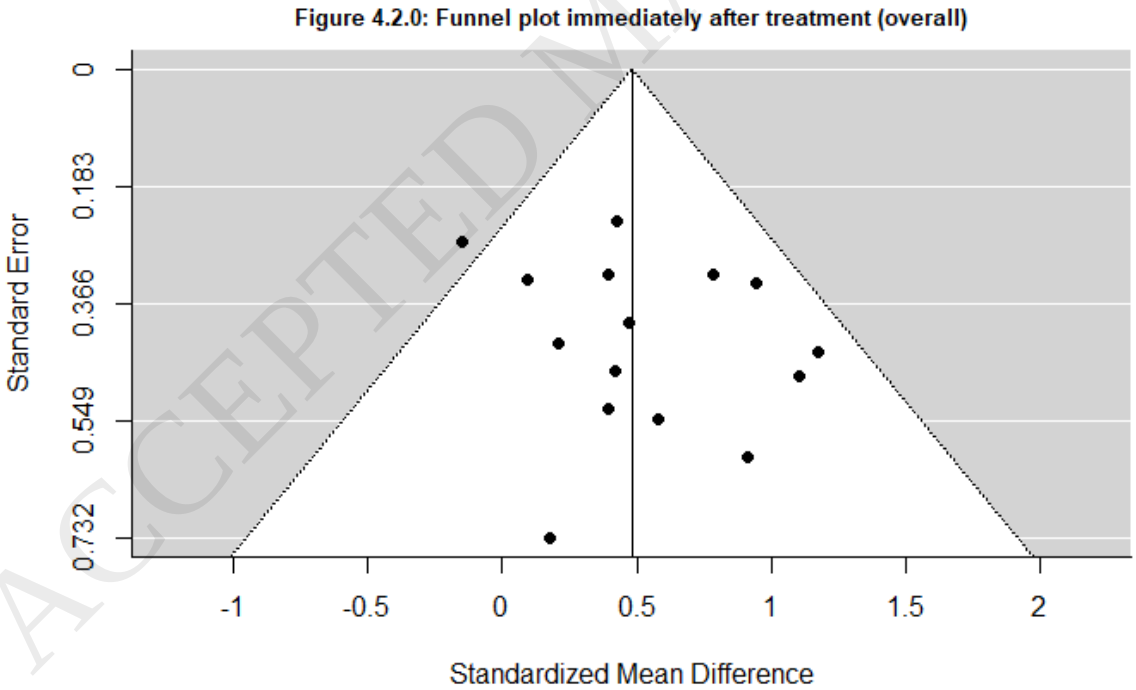


Figure 4.2.1: Trim and fill funnel plot immediately after treatment (TMS only)

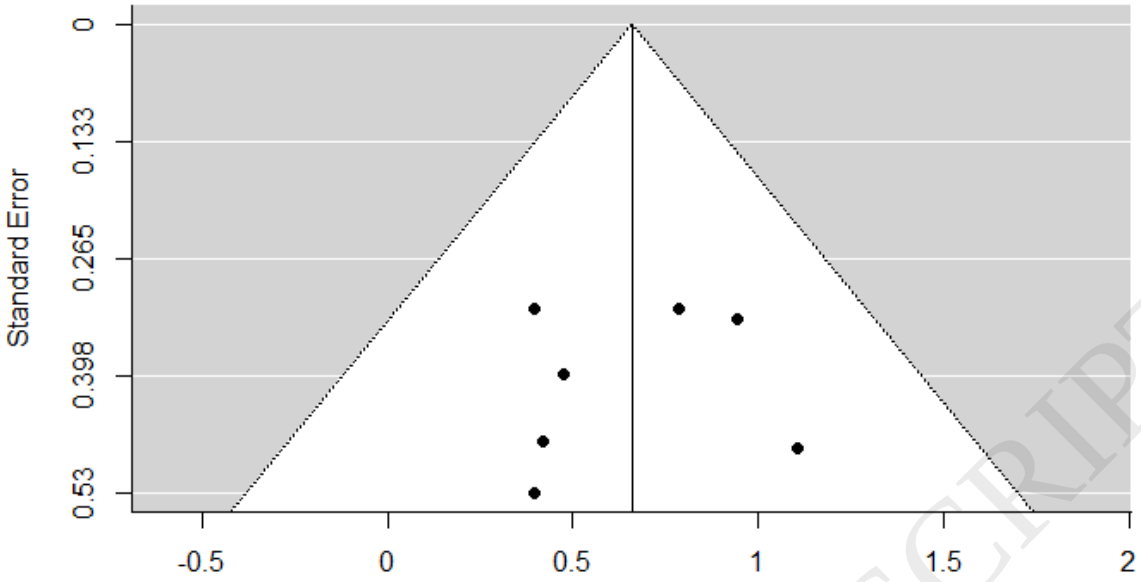


Figure 4.2.1: Trim and fill funnel plot immediately after treatment (TMS only)

Figure 4.2.2: Trim and Fill Funnel plot of tDCS After

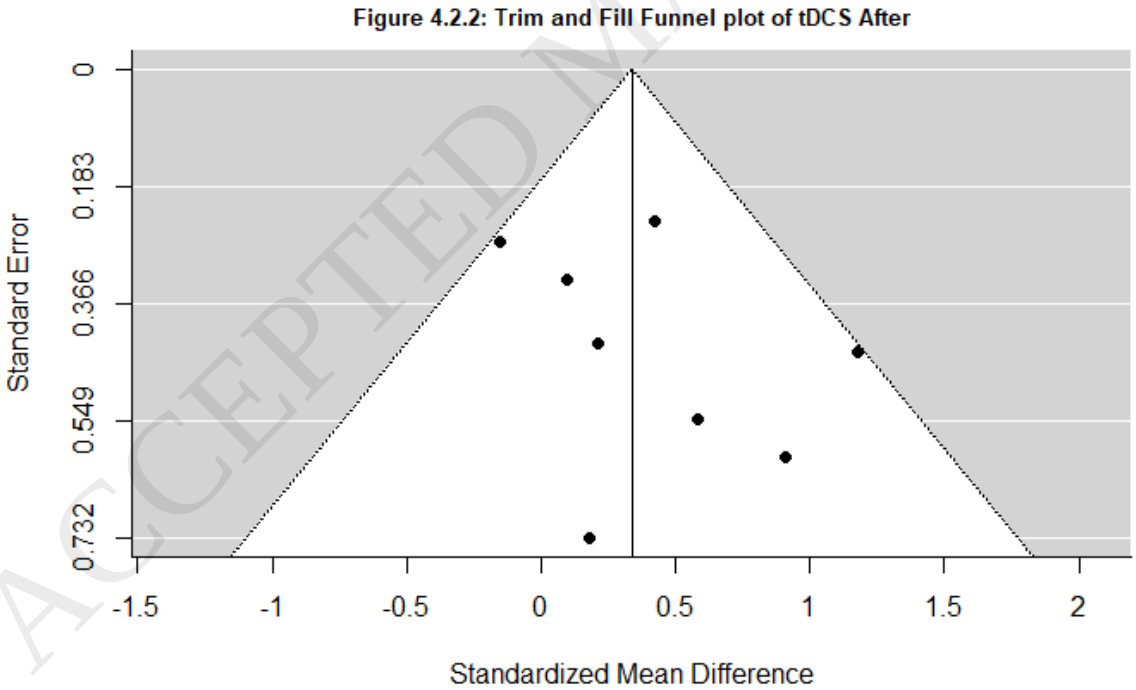


Figure 5: Forest plot of chronic subgroup effect sizes at follow-up, broken down by NIBS (TMS vs. tDCS)

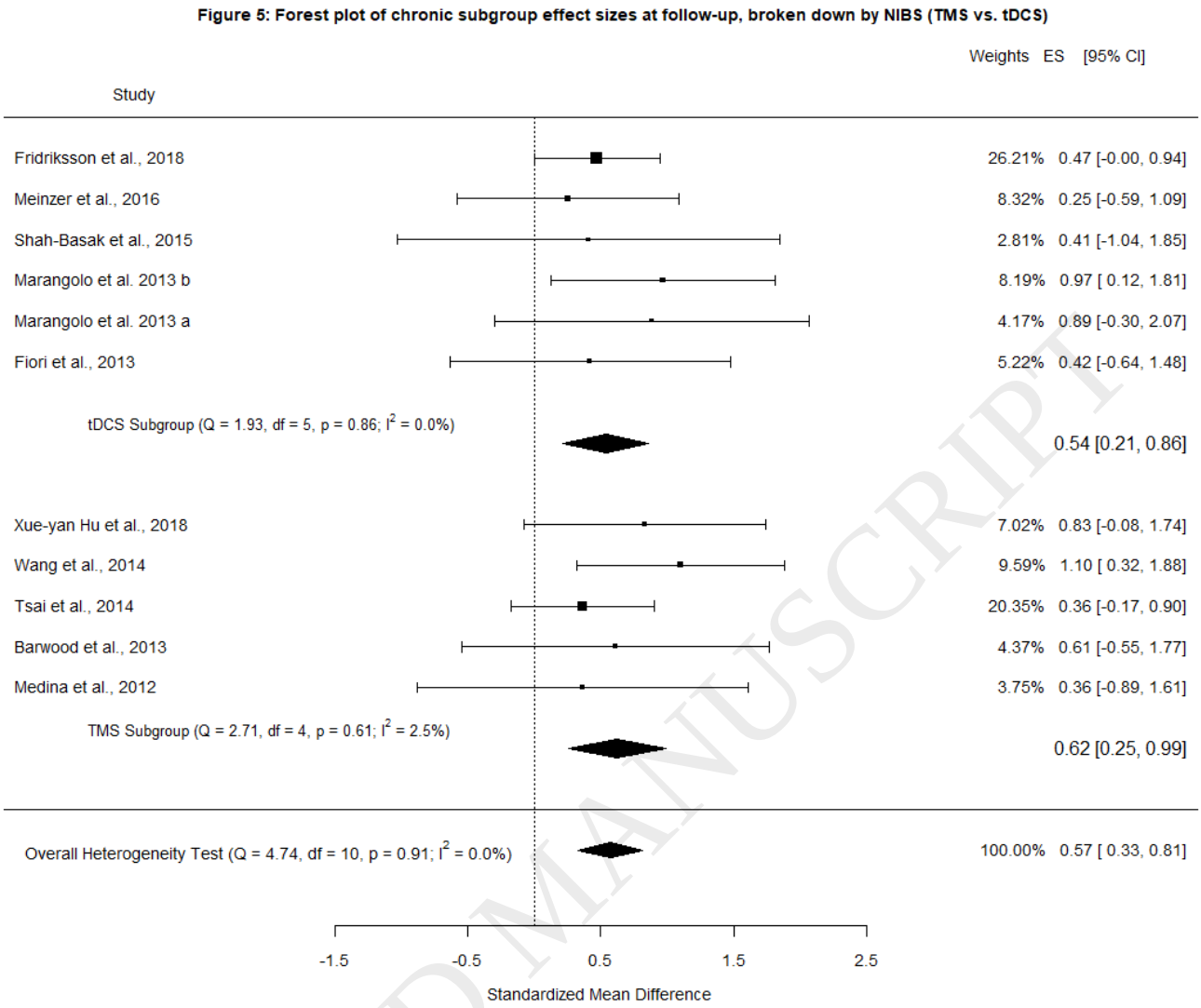


Figure 5.1.0: Baujat plot of chronic subgroup at follow-up (TMS & tDCS)

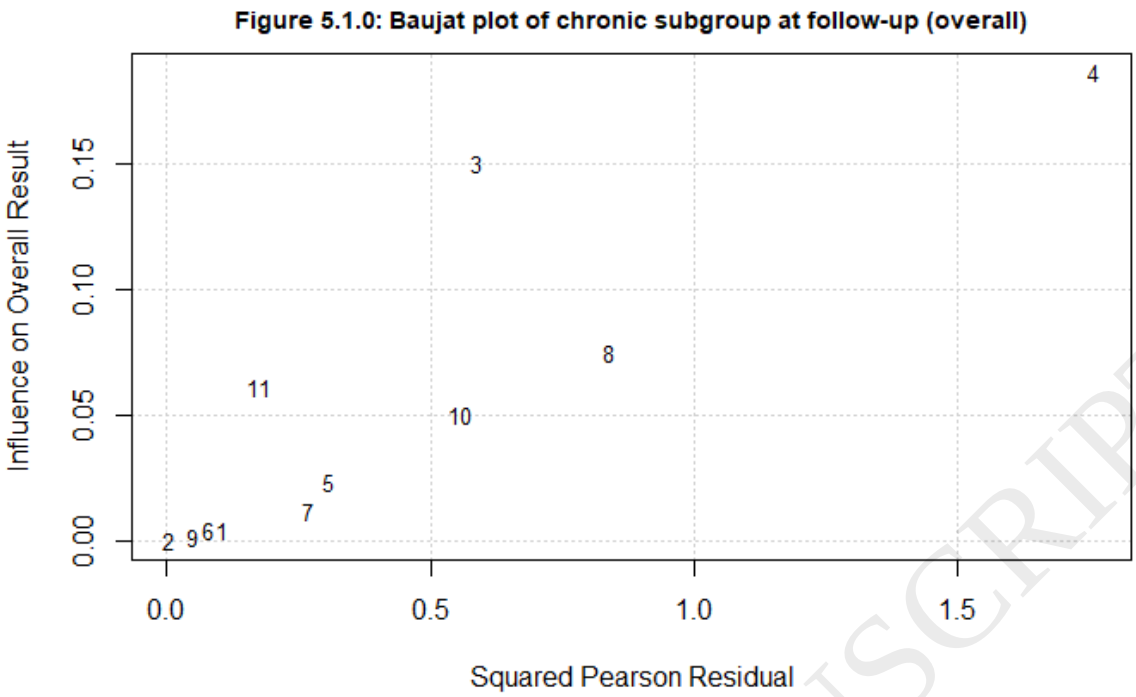


Figure 5.1.1: Baujat plot of chronic subgroup at follow-up (TMS only)

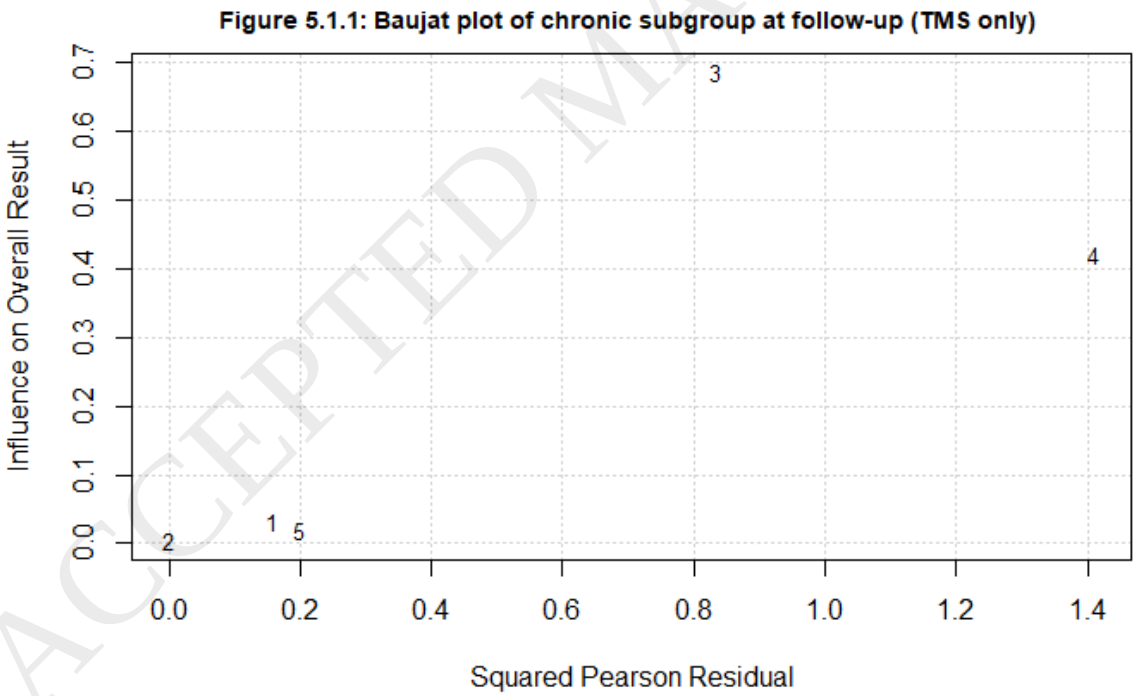


Figure 5.1.2: Baujat plot of chronic subgroup at follow-up (tDCS only)

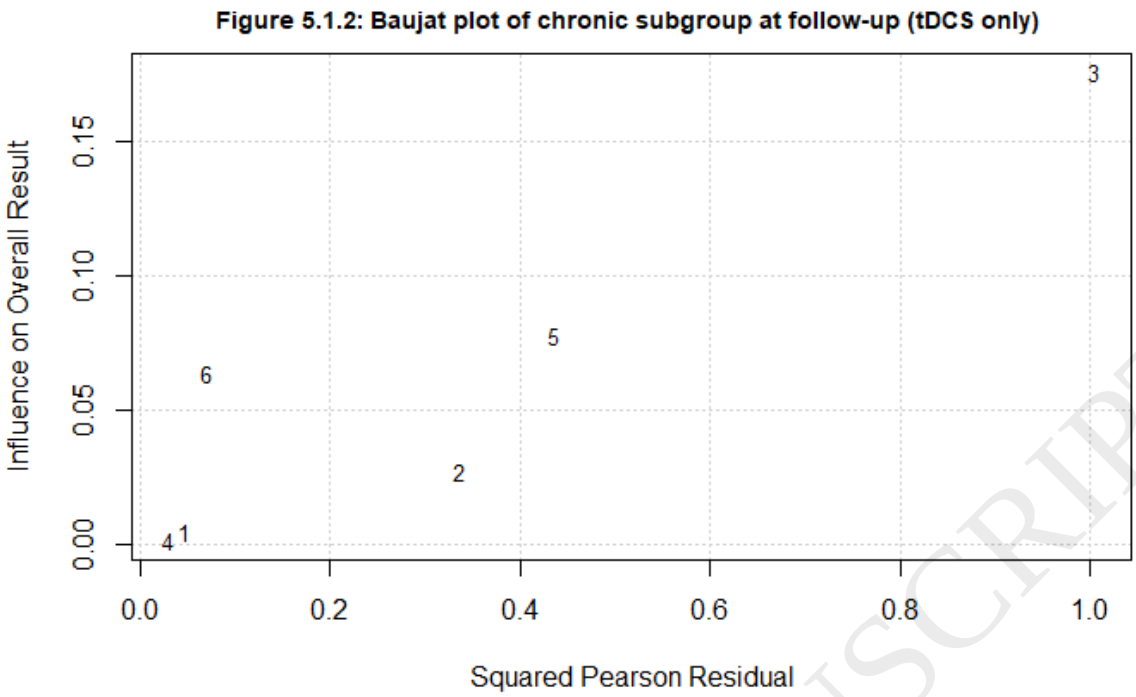


Figure 5.2.0: Publication bias assessed by funnel plot of chronic subgroup (TMS & tDCS)

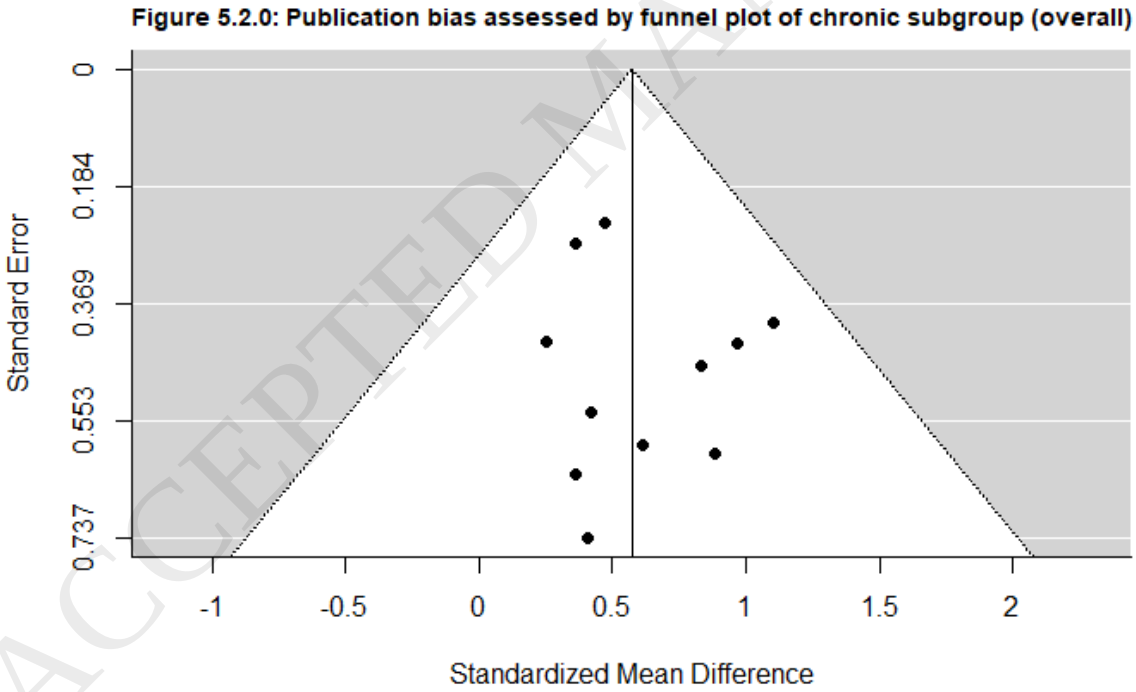


Figure 5.2.1: Funnel plot of chronic subgroup at follow-up (TMS only)

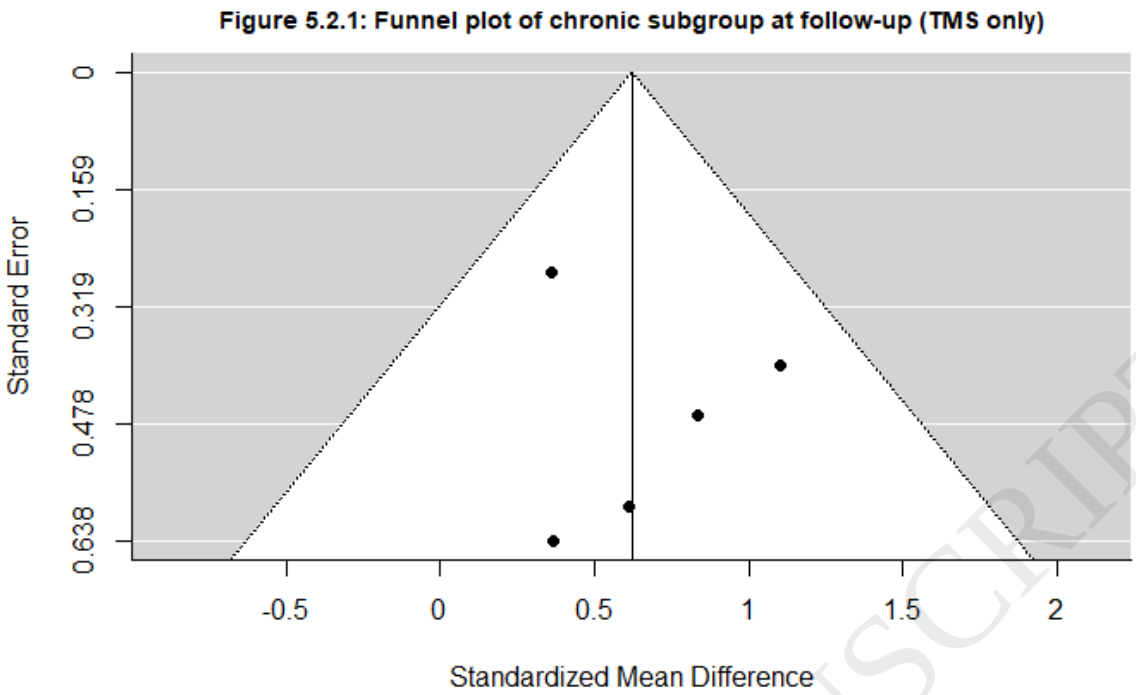


Figure 5.2.2: Funnel plot of chronic subgroup at follow-up (tDCS only)

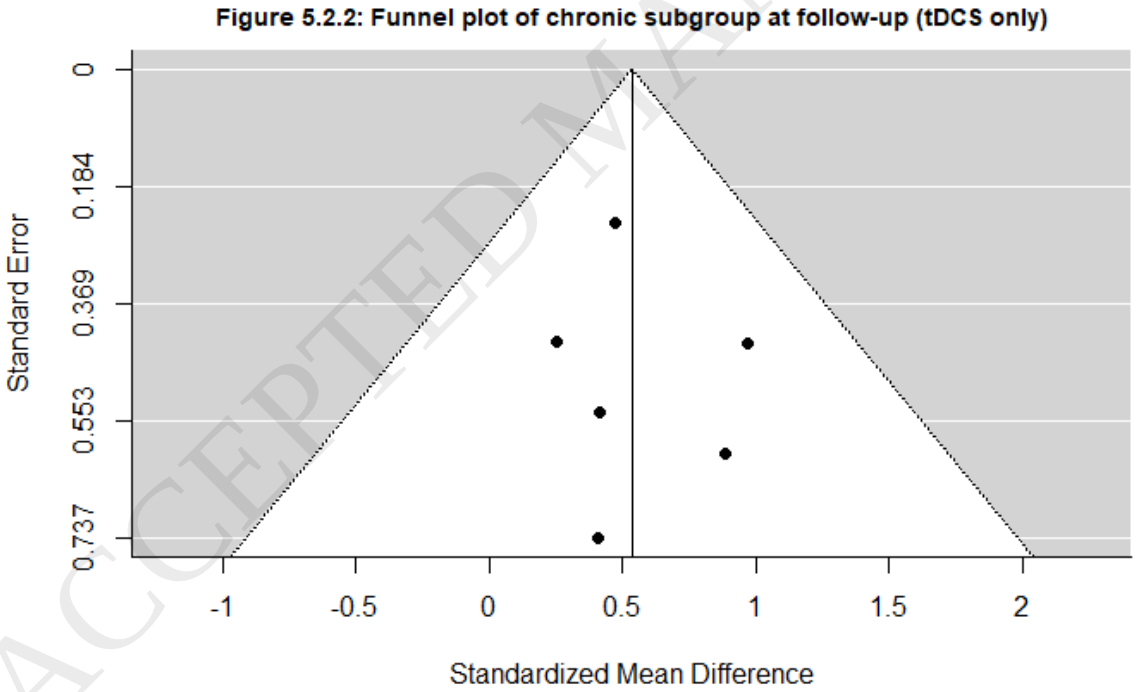


Figure 6: Forest plot of subacute subgroup effect sizes at follow-up, TMS and tDCS

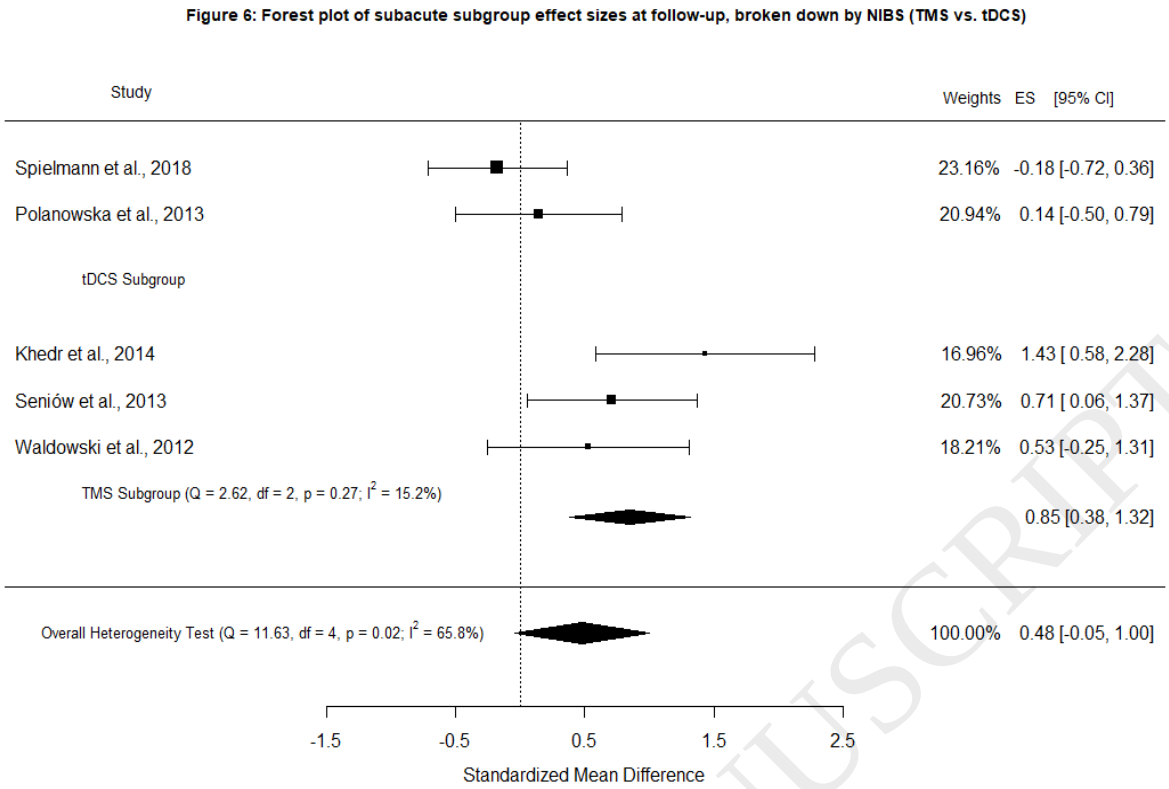


Figure 6.1.0: Baujat plot of subacute subgroup at follow-up (TMS & tDCS)

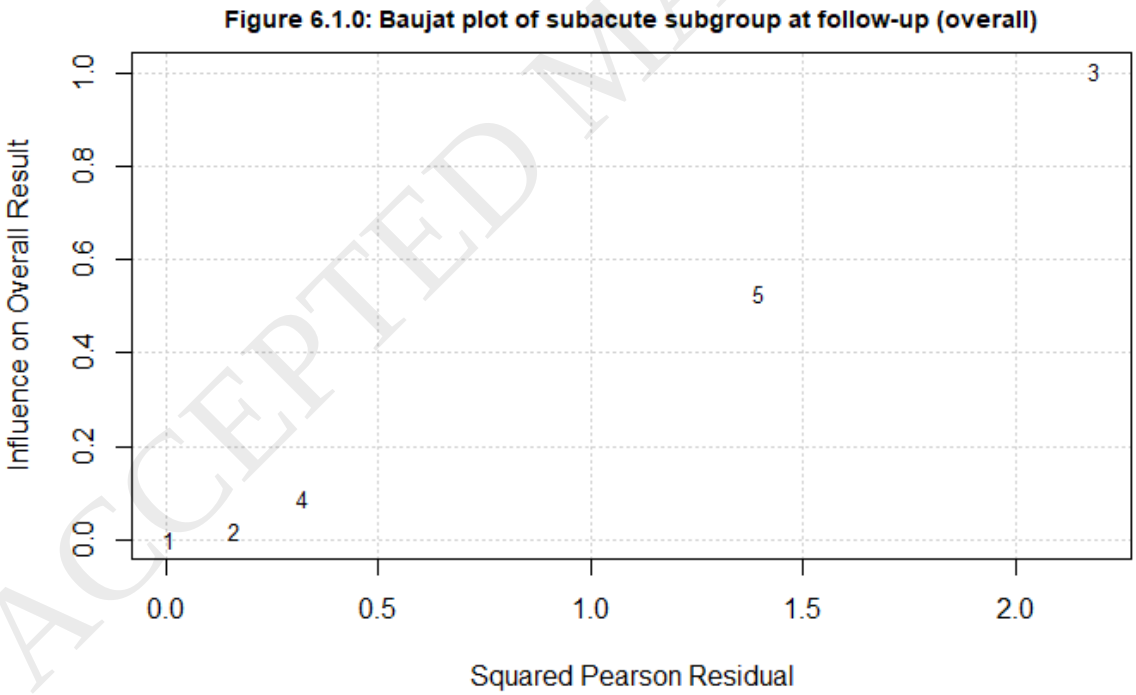


Figure 6.1.1: Baujat plot of subacute subgroup at follow-up (TMS only)

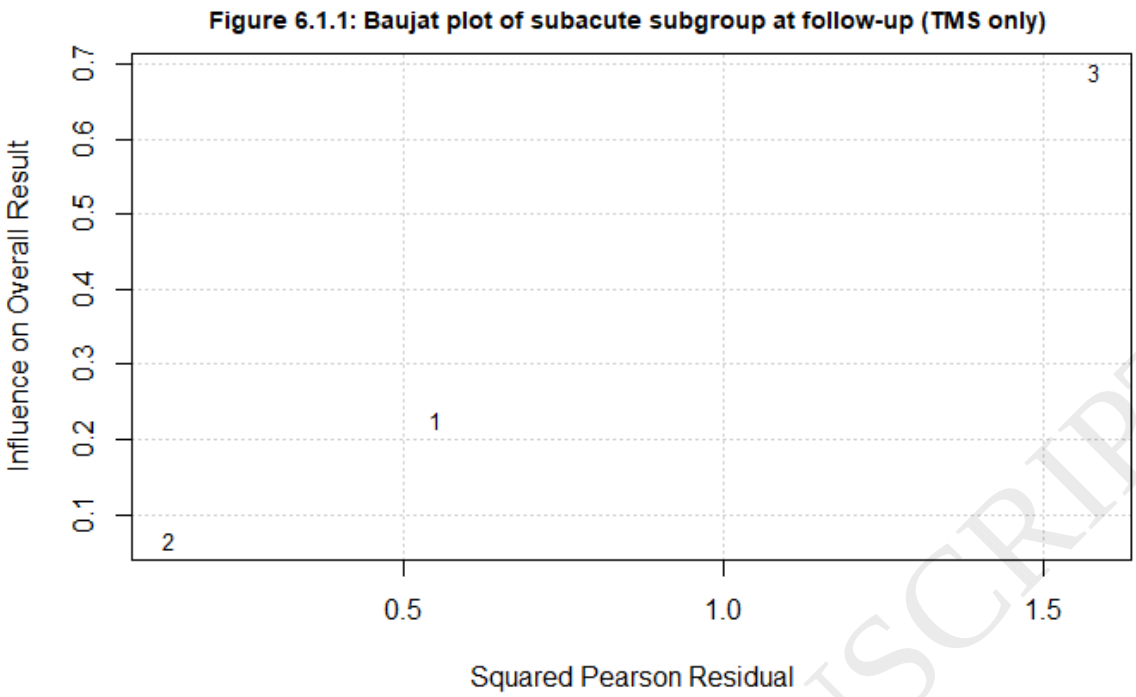


Figure 6.2.0: Trim and fill funnel plot of subacute subgroup (TMS & tDCS)

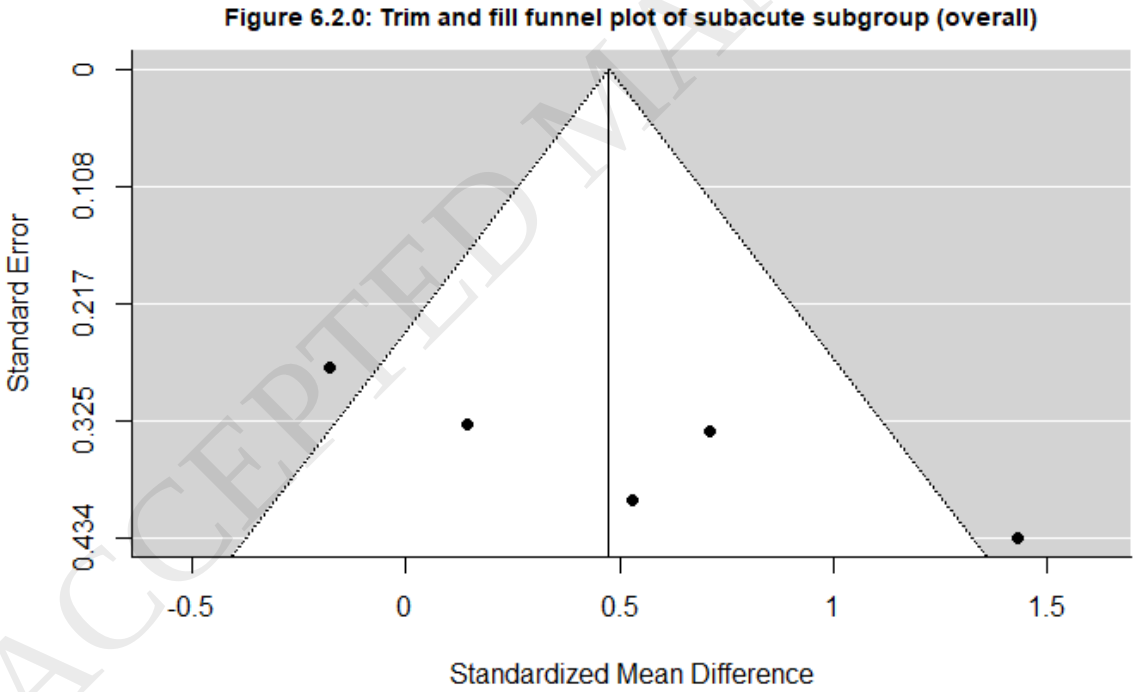


Figure 6.2.1: Funnel plot of subacute subgroup at follow-up (TMS only)

**Figure 6.2.1: Funnel plot of subacute subgroup at follow-up (TMS only)**

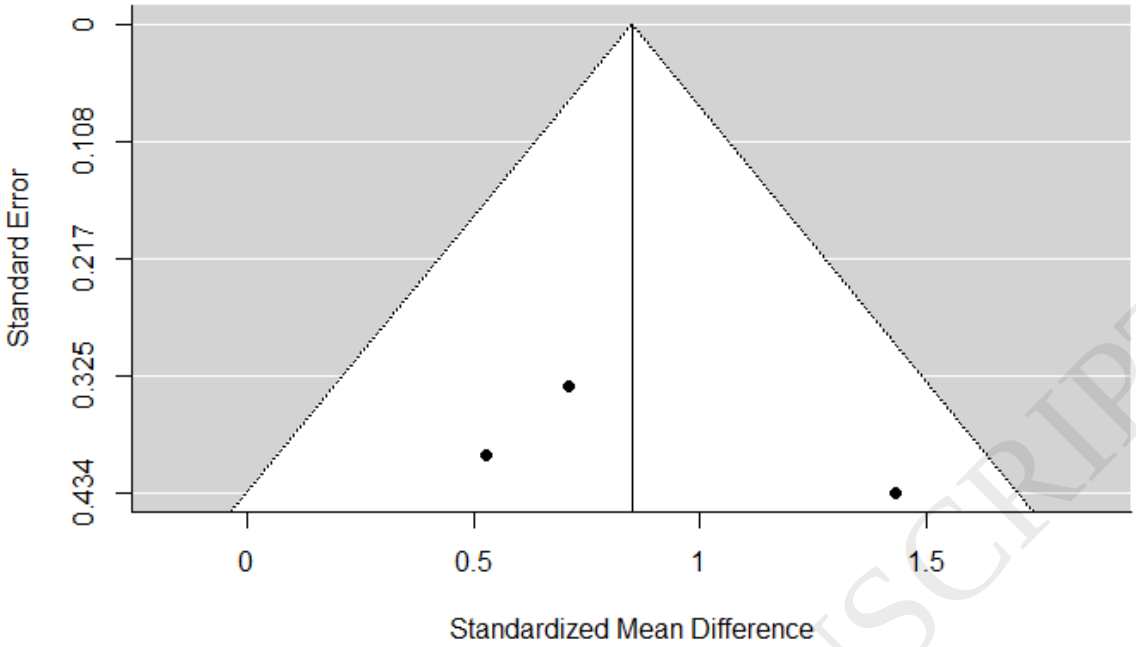

**Table 1. Summary of patients' characteristics**

| ID | Study | NIBS | Overall sample size | Experimental group characteristics | | | | | | | Control group | Drop out |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Sample Size | Male | Female | Mean Age (SD) | Stroke Interval Chronic/Subacute | Mean Stroke Interval | Handedness | Sample Size | |
| 1 | Waldowski et al., 2012 [84] | TMS | 26 | 13 | 6 | 7 | 62.31 ± 11.03, range 38 - 77 | subacute | 28.92 ± 19.39 days | right | 13 | 0 |
| 2 | Medina et al., 2012 [91] | TMS | 10 | 5 | 4 | 1 | 60.60 ± 7.1, range 51- 71 | chronic | 49.8 ± 29.6, range 6-87 months | right | 5 | 0 |
| 3 | Barwood et al., 2013 [85] | TMS | 12 | 6 | 4 | 2 | 61 ± 7.5, range 54-66 | chronic | 44.4 ± 15.08, range 31-69 months | right | 6 | 0 |
| 4 | Seniów et al., 2013 [86] | TMS | 38 | 19 | 8 | 11 | 61,65 ± 11.7, range 38-73 | subacute | 33.4 ± 24.18, range 11-106 days | right | 19 | 2 |
| 5 | Khedr et al., 2014 [87] | TMS | 29 | 19 | 8 | 11 | 61 ± 9.8 | subacute | 40.6 ± 28.50 days | right | 10 | 1 |
| 6 | Tsai et al., 2014 [88] | TMS | 53 | 31 | 22 | 9 | 62.3 ± 12.1 | chronic | 17.8 ± 7.2 months | right | 22 | 3 |
| 7 | Wang et al., 2014 [89] | TMS | 29 | 15 | 14 | 1 | 61.3 ± 13.2 | chronic | 16.8 ± 6.4 months | right | 14 | 0 |
| 8 | Xue-yan Hu et al., 2018 [90] | TMS | 20 | 10 | 6 | 4 | 48.5± 11.2 | chronic | 7.5 ± 3.2 months | right | 10 | 0 |
| 9 | Fiori et al., 2013 [80] | tDCS | 7 | **7** | 5 | 2 | 58.4 ± 9.5, range 44-71 | chronic | 33.8 ± 27.9, range 7-84 months | right | **7** | 0 |
| 10 | Marangolo et al. 2013 a [81] | tDCS | 7 | **7** | 5 | 2 | 62.4 ± 9.5, range 46-77 | chronic | 40.8 ± 26.7, range 7 - 84 months | right | **7** | 1 |
| 11 | Marangolo et al. 2013 b [82] | tDCS | 12 | **12** | 8 | 4 | 59.5 ± 8.14, range 44-71 | chronic | 37.25 ± 22.15, range 7 - 84 months | right | **12** | 0 |
| 12 | Polanowska et al., 2013 [76] | tDCS | 37 | 18 | 11 | 7 | 57.6 ± 9.6, range 34-75 | subacute | 55.7 ± 44.8, range 10-187 days | right | 19 | 4 |
| 13 | Shah-Basak et al., 2015 [83] | tDCS | 5 | **5** | ns | ns | 63.6 ± 8.6, range 53-78 | chronic | 31 ± 29.7, range 7-101 months | right | **3** | 2 |
| 14 | Meinzer et al., 2016 [77] | tDCS | 26 | 13 | 7 | 6 | 59.9± 11.8, range 38 - 77 | chronic | 46±24.5, range: 15-108 months | right | 13 | 0 |
| 15 | Spielmann et al., 2018 [78] | tDCS | 54 | 23 | 18 | 5 | 57.9± 9.6 | subacute | 46.9±16.1 days | right | 31 | 4 |
| 16 | Fridriksson et al., 2018 [79] | tDCS | 74 | 34 | 24 | 10 | 60± 11 | chronic | 44± 45 months | right | 40 | 8 |

Abbreviations: NIBS, noninvasive brain stimulation methods; SD, standard deviation; tDCS, Transcranial direct current stimulation; TMS, transcranial magnetic stimulation

* NOTE: the bolded numbers indicate that the same patients were in the treatment and control group, as part of open crossover designs.

**Table 2. Summary of disorders' characteristics**

| | Study | NIBS | Lesion area | Lesion Type | Aphasia Type | Diagnosis criteria and instruments | Aphasia Severity | Outcome | Outcome Evaluation |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Waldowski et al., 2012 | TMS | anterior and posterior language areas | ischemic stroke | all types | BDAE, ASRS | moderate to severe | Naming | Computerized Picture Naming Test (Accuracy) |
| 2 | Medina et al., 2012 | TMS | left insula, Heschl's gyrus, and Rolandic operculum | ischemic stroke | non fluent | BDAE, BNT, Snodgrass & Vanderwart picture inventory | mild to moderate | Speech | Cookie Theft description: Correct Information Units (Discourse Productivity) |
| 3 | Barwood et al., 2013 | TMS | left MCA territory (for details see Table 1 - the Barwood et al., 2013 study) | ischemic stroke | non fluent | BDAE, BNT, Snodgrass & Vanderwart picture inventory | mild to severe | Naming | BNT mean scores |
| 4 | Seniów et al., 2013 | TMS | left MCA territory (for details see Table 1 - Seniów et al., 2013 study) | ischemic stroke | all types | BDAE, ASRS | moderate to severe | Naming | BDAE (Naming subtest) |
| 5 | Khedr et al., 2014 | TMS | cortical and subcortical areas | ischemic stroke | non fluent | BDAE, ASRS | mild to severe | Naming | HSS naming score (changes in mean) |
| 6 | Tsai et al., 2014 | TMS | left hemisphere (not better specified) | ischemic stroke | non fluent | Picture Naming Test, Concise Chinese Aphasia Test | mild to severe | Naming | Object and Action Naming accuracy (%) |
| 7 | Wang et al., 2014 | TMS | left MCA territory | ischemic stroke | non fluent | Picture Naming Test, Concise Chinese Aphasia Test | NS | Naming | Object and Action Naming accuracy (%) |
| 8 | Xue-yan Hu et al., 2018 | TMS | left MCA territory | ischemic or hemorrhagic stroke | non fluent | WAB | NS | Naming | WAB- Chinese version (Naming subtest) |
| 9 | Fiori et al., 2013 | tDCS | left temporal cortex, left temporal-insular region, frontotemporal cortices (for details see Figure 1 - Fiori et al., 2013 study) | ischemic stroke | non fluent | BADA; Token test | NS | Naming | Mean percentage of response accuracy for nouns and verbs |
| 10 | Marangolo et al. 2013 a | tDCS | superior temporal gyrus, frontotemporal cortices and part of the parietal cortex (for details see Figure 1 - Marangolo et al. 2013 a study) | ischemic stroke | non fluent | BADA | NS | Naming | Mean percentage of correct responses |
| 11 | Marangolo et al. 2013 b | tDCS | capsula estrema, claustrum, part of the capsula esterna and putamen, inferior frontal gyrus and superior temporal gyrus (for details see Figure 1 - Marangolo et al. 2013 b study) | ischemic stroke | non fluent | BADA; Token test | NS | Speech | Mean percentage of correct Content Units |
| 12 | Polanowska et al., 2013 | tDCS | frontal, temporal, parietal, occipital, insular, subcortical (for details see Table 1 - Polanowska et al., 2013 study) | ischemic stroke | all types | BDAE, ASRS | moderate to severe | Naming | BDAE Naming |
| 13 | Shah-Basak et al., 2015 | tDCS | left MCA territory, IFG, STG (for details see Table 1 - Shah-Basak et al., 2015 study) | stroke | non fluent | WAB | mild to severe | WAB-AQ | Mean WAB-AQ scores |
| 14 | Meinzer et al., 2016 | tDCS | left MCA territory (for details see Figure 3 and Table 1 - Meinzer et al., 2016 study) | ischemic or hemorrhage stroke | all types | AAT | NS | Naming | Naming untrained items |
| 15 | Spielmann et al., 2018 | tDCS | left hemisphere (not better specified) | ischemic or hemorrhage stroke | all types | Shortened token test | mild to severe | Naming | Boston Naming Test |
| 16 | Fridriksson et al., 2018 | tDCS | left hemisphere (not better specified) | ischemic or hemorrhage stroke | all types | WAB-R | mild to severe | Naming | Change in Correct Naming |

Abbreviations: MCA, Middle cerebral artery; IFG, Inferior frontal gyrus; STG, Superior temporal gyrus; AAT, Aachener Aphasie Test; ASRS, Apraxia of Speech Rating Scale; BADA, Battery for the Assessment of Aphasic Deficits; BDAE, Boston Diagnostic Aphasia Examination; BNT, Boston Naming Test; HSS, Hemispheric Stroke Scale; NS, not specified; PALPA, Psycholinguistic assessments of language processing in aphasia;SLTA, Standard Language Test of Aphasia; tDCS, Transcranial direct current stimulation; TMS, transcranial magnetic stimulation; WAB, Western Aphasia Battery; WAB-AQ, WAB Aphasia Quotient; WAB-R, Western Aphasia Battery – Revised;

**Table 3 Summary of TMS study characteristics**

| | Study | Target area(s) | | TMS Stimulation Parameters | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Anterior/Posterior areas | RH/LH (contralateral /ipsilateral) | rTMS Frequency | Intensity (% RMT) | Number of pulses and duration | Number of sessions | Online/Offline Stimulation & Therapy | Sham | Adverse Effects |
| 1 | Waldowski et al., 2012 | Anterior: Broca's homologue | RH(contralateral) | 1 HZ inhibitory | 90% RMT | 1800 pulses (900 PTr, 900 POp), 30 min (15 min PTr , 15 min POp) | 15 sessions (5 days x 3 weeks) | offline with speech and language therapy | air-cooled sham coil | no adverse effect related to rTMS |
| 2 | Medina et al., 2012 | Anterior: pars triangularis (n=9) or pars orbitalis (n=1); (best response area between BA 44, BA 45, BA 47) | RH(contralateral) | 1 HZ inhibitory | 90% RMT | 1200 pulses, 20 min | 10 sessions (5 days x 2 weeks) | only TMS | coil perpendicular to the scalp | all subjects tolerated stimulation without complaint of physical discomfort or other adverse effects |
| 3 | Barwood et al., 2013 | Anterior: Broca's homologue (rPTr) | RH(contralateral) | 1 HZ inhibitory | 90% RMT | 1200 pulses, 20 min | 10 sessions (5 days x 2 weeks) | only TMS | sham coil | ns |
| 4 | Seniów et al., 2013 | Anterior: Broca's homologue | RH(contralateral) | 1 HZ inhibitory | 90% RMT | 1800 pulses, 30 min | 15 sessions (5 days x 3 weeks) | offline with speech and language therapy | air-cooled sham coil | patients tolerated rTMS well, and no adverse effects were observed |
| 5 | Khedr et al., 2014 | Anterior: PTr, POp | both *RH (contralateral) and * *LH (ipsilateral)* | *1 HZ inhibitory ** *20 HZ excitatory* | *110% RMT, ***80% RMT* | * 1000 pulses (500 PTr, 500 POp), ***10 trains (5 PTr, 5 POp) of 5 seconds each with an inter-train interval of 30 seconds* | 10 sessions (5 days x 2 weeks) | offline with language therapy | coil rotated at 90° away from the scalp | no patient developed seizures during the study or on follow-up |
| 6 | Tsai et al., 2014 | Anterior: rPTr | RH(contralateral) | 1 HZ inhibitory | 90% RMT | 600 pulses, 10 min | 10 sessions (5 days x 2 weeks) | offline with speech therapy | sham coil | no subjects reported any adverse effects during the study or after the 3-month follow-up |
| 7 | Wang et al., 2014 | Anterior: rPTr | RH(contralateral) | 1 HZ inhibitory | 90% RMT | 1200 pulses, 20 min | 10 sessions (5 days x 2 weeks) | online with picture-naming training | sham coil | one patient in the TMS group reported a dull pain at first when placed under the activated coil, but the discomfort subsided once the stimulation intensity was reduced by 5% |
| 8 | Xue-yan Hu et al., 2018 (1 Hz) | Anterior: Broca's homologue | RH(contralateral) | 1 HZ inhibitory | 80% RMT | 600 pulses, 10 min | 10 sessions | offline with language therapy | coil rotated at 90° away from the scalp | NS |

Abbreviations: BA, Brodmann area; LH, left hemisphere; min, minutes; NS, not specified; POp, pars opercularis; PTr, pars triangularis; rPTr, right pars triangularis; rIFG, right inferior frontal gyrus; RH, right hemisphere; rPOrb, right pars orbitalis; RMT, resting motor threshold; rTMS, repetitive transcranial magnetic stimulation; rSTG, right superior temporal gyrus.

**Table 4 Summary of tDCS study characteristics**

| ID | Study | tDCS Stimulation Parameters | | | | | | | | Sham | Adverse Effects. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Montage Unipolar /Bipolar (A-tDCS, C-tDCS) | Stimulation Area, Electrode Position | | Reference Electrode | Electrode dimension | Current Intensity | Number of stimulations Duration | Online/ Offline Stimulation & Therapy | | |
| 1 | Fiori et al., 2013 | Unipolar (A-tDCS) | Anterior: anodic (F5-A) Broca's area | LH (ipsilateral) | cathode: contralateral fronto-polar cortex | 5×7cm | 1 mA, current density = 0.028 | 20min, 5 daily sessions | online with naming task | turned off after 30 s | NS |
| 2 | Marangolo et al. 2013 a | Unipolar (A-tDCS) | Anterior: anodic (F5-A) Broca's area | LH (ipsilateral) | cathode: contralateral fronto-polar cortex | 5×7cm | 1 mA, current density = 0.028 | 20min, 5 daily sessions | online with naming task | turned off after 30 s | NS |
| 3 | Marangolo et al. 2013 b | Unipolar (A-tDCS) | Anterior: anodic (F5-A) Broca's area | LH (ipsilateral) | cathode: contralateral fronto-polar cortex | 5×7cm | 1 mA, current density = 0.028 | 20min, 10 daily sessions | online with conversational therapy | turned off after 30 s | NS |
| 4 | Polanowska et al., 2013 | Unipolar (A-tDCS) | Anterior: anodic Broca's area | LH (ipsilateral) | cathode: right supraorbital area | 5×7cm | 1 mA, current density = 0.028 | 10 min, 15 daily sessions | offline, language therapy sessions after tDCS | turned off after 15 s | NS |
| 5 | Shah-Basak et al., 2015 | Unipolar (A-tDCS or C-tDC to the right or left hemisphere): best response at one of the four active montages (see text) (Phase 1) | Anterior: n=3: left-frontal anode, n=3 left-frontal cathode, n=1 right-frontal cathode | RH or LH (contralateral or ipsilateral) | anode or cathode: contralateral mastoid | 5×5 cm | 2 mA, current density = 0.08 | 20 min, 10 days sessions | online, picture-naming task | turned off after 1 minute | NS |
| 6 | Meinzer et al., 2016 | Unipolar (A-tDCS ) | Anterior: anodic left M1 | LH (ipsilateral) | cathode: right supraorbital region | anode 5 x7 cm, cathode 10 x10 cm | 1 mA, current density = 0.028 | 20 min, 16 sessions in 8 days (2 x 1.5 h/day) | online, computer-assisted naming treatment | turned off after 30 s | Only mild sensations (e.g. itching, tingling, slight burning feeling) during the initial ramping up were reported |
| 7 | Spielmann et al., 2018 | Unipolar (A-tDCS ) | Anterior: anodic left -IFG | LH (ipsilateral) | cathode: right supraorbital region | 5 x 7 cm | 1 mA, current density = 0.028 | 20 min, 10 sessions (2 week | online, word-finding therapy | turned off after 30 s | Sixty-nine percent reported no pain (score=0); the rest reported very little pain/ little pain (score=1–2), 56% of these participants received sham- tDCS. There was no significant difference in pain rating |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | s x 5 days) | | | between groups. Reported side effects were headache and skin irritability; no adverse events were reported during treatment. |
| 8 | Fridriksson et al., 2018 | Unipolar (A-tDCS ) | Posterior: anodic temporal lobe region with the highest naming-related activation on fMRI | LH (ipsilateral) | cathode: right supraorbital region | 5×5 cm | 1 mA, current density = 0.04 | 20min, 15 sessions (3 weeks x 5 days) | online with naming task | turned off after 30 s | Headache - 2 (S-tDCS), Dizziness - 1 (A-tDCS), 2 (S-tDCS), Erythema - 2 (A-tDCS), Convulsion (S-tDCS), Hypertension - 1 (S-tDCS) |

Abbreviations: A-tDCS, anodal transcranial direct current stimulation; C-tDCS, cathodal tDCS; S-tDCS, Sham tDCS; IFG, inferior frontal gyrus; L-IFG, left IFG; R-IFG, right IFG; STG, superior temporal gyrus; R-STG, right STG; L-STG, left STG; M1, primary motor cortex; fMRI, Functional Magnetic Resonance Imaging; LH, left hemisphere; RH, right hemisphere; NS, not specified.

**Table 5.1 Summary of the TMS studies' characteristics:**

| N | Study | Study main objective | Study language | Study Arms for the meta-analysis | Follow-up | Results/ Author's Conclusion | Study design | Levels of evidence modified Sackett Scale |
|---|---|---|---|---|---|---|---|---|
| 1 | Waldowski et al., 2012 | Effect of Low-Frequency Repetitive Transcranial Magnetic Stimulation on Naming Abilities in Early-Stroke Aphasic Patients: A Prospective, Randomized, Double-Blind Sham-Controlled Study | whether low-frequency rTMS over the Broca's homologues in combination with speech/language therapy improves naming in early-stroke aphasia patients | Polish | TMS VS sham | **15 weeks** | all groups improved but there was no significant difference in average test scores between groups at any time point | RCT | Level 1b |
| 2 | Medina et al., 2012 | Finding the Right Words: Transcranial Magnetic Stimulation Improves Discourse Productivity in Non-fluent Aphasia After Stroke | whether rTMS improves fluency in individuals with chronic non-fluent aphasia, and to identify aspects of fluency that are modulated in persons who respond to rTMS | English | TMS VS sham | **2 months** | trends toward greater changes from baseline in subjects receiving rTMS compared to sham (low statistical power) | Randomized, Partial Crossover (2 months of intersession interval) | Level 1b |
| 3 | Barwood et al., 2013 | Long term language recovery subsequent to low frequency rTMS in chronic non-fluent aphasia | to assess the efficacy of inhibitory rTMS in modulating language performance in non-fluent aphasia | English | TMS VS sham | 1 week, **2 months**, 8 months, 12 months | rTMS > Sham for naming, expressive language and auditory comprehension | RCT | Level 1b |
| 4 | Seniów et al., 2013 | Transcranial Magnetic Stimulation Combined with Speech and Language Training in Early Aphasia Rehabilitation: A Randomized Double-Blind Controlled Pilot Study | whether rTMS inhibiting the right-hemisphere Broca's area homologue improves language restitution if combined with speech/language therapy | Polish | TMS VS sham | **15 weeks** | rTMS was not effective for all post-stroke aphasia patients, although it might benefit selected patients | RCT | Level 1b |
| 5 | Khedr et al., 2014 | Dual-Hemisphere Repetitive Transcranial Magnetic Stimulation for Rehabilitation of Post-stroke Aphasia: A Randomized, Double- Blind Clinical Trial | to evaluate the long-term efficacy of dual-hemisphere rTMS on post-stroke aphasia | Egyptian | TMS VS sham | 1 month, **2 months** | greater improvement in the language scores after real rTMS compared with sham rTMS | RCT | Level 1b |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 6 | Tsai et al., 2014 | The Persistent and Broadly Modulating Effect of Inhibitory rTMS in Non-fluent Aphasic Patients: A Sham-Controlled, Double-Blind Study | whether 1Hz rTMS improves language performance and to identify characteristics of patients who can benefit most from this treatment | Mandarin Chinese | TMS VS sham | **3 months** | inhibition of the contralesional pars triangularis enhances language recovery | RCT | Level 1b |
| 7 | Wang et al., 2014 | Efficacy of Synchronous Verbal Training During Repetitive Transcranial Magnetic Stimulation in Patients With Chronic Aphasia | the efficacy of synchronous speech therapy integrated with an rTMS protocol | Chinese | TMS VS sham | **3 months** | rTMS and language training can be combined to achieve outcomes superior to those obtained when used separately | RCT | Level 1b |
| 8 | Xue-yan Hu et al., 2018 (1 HZ) | Effects of different frequencies of repetitive transcranial magnetic stimulation in stroke patients with non-fluent aphasia: a randomized, sham-controlled study | to compare the efficacy of rTMS applied at different frequencies to the contralesional hemisphere, to optimize the treatment of post-stroke non-fluent aphasia | Chinese | LF-TMS VS sham | **2 months** | LF-rTMS and HF-rTMS are both beneficial to the recovery of linguistic function in patients with post-stroke non-fluent aphasia | RCT | Level 1b |

**Table 5.2 Summary of the tDCS studies' characteristics:**

| N | Study | Study main objective | Study language | Study Arms for the meta-analysis | Follow-up | Results/ Author's Conclusion | Study design | Levels of evidence (PEDro) |
|---|---|---|---|---|---|---|---|---|
| 9 | Fiori et al., 2013 (Broca) | tDCS stimulation segregates words in the brain: evidence from aphasia | whether tDCS, over the left frontal and the temporal regions coupled with an intensive language treatment, would differently improve noun and verb recovery in chronic aphasia | Italian | Broca tDCS VS sham | 1 week, **4weeks** | greater improvement in object naming after tDCS | Randomized Crossover (6 days of interses sion interval) | Level 2 |
| 10 | Marangolo et al. 2013a (Broca) | Differential involvement of the left frontal and temporal regions in verb naming: A tDCS treatment study | to determine whether coupling tDCS with an intensive language treatment would improve verb retrieval deficits in chronic aphasic | Italian | Broca tDCS VS sham | 2 weeks, **4weeks** | better response accuracy during the anodic tDCS over Broca's area VS tDCS over Wernicke or VS Sham | Randomized Crossover (6 days of interses sion interval) | Level 2 |
| 11 | Marangolo et al. 2013b (Broca) | tDCS over the left inferior frontal cortex improves speech production in aphasia | to investigate the combined effect of tDCS and intensive Conversational therapy on discourse skills in chronic aphasia | Italian | Broca tDCS VS sham | **4weeks** | anodic tDCS over Broca's area together with intensive "Conversational Therapy" improves informative speech | Randomized Crossover (14 days of interses sion interval) | Level 2 |
| 12 | Polanowska et al., 2013 | No effects of anodal transcranial direct stimulation on language abilities in early rehabilitation of post-stroke aphasic patients | the effectiveness of A-tDCS over Broca's area to enhance aphasia recovery during early post-stroke rehabilitation | Polish | Broca tDCS VS sham | **3 months** | the results did not confirm a positive impact of repeated A-tDCS, preceding language therapy, on language abilities | RCT | Level 1b |
| 13 | Shah-Basak et al., 2015 | Individualized treatment with transcranial direct current stimulation in patients with chronic non-fluent aphasia due to stroke | whether tDCS with an individualized optimal montage could lead to persistent reduction of aphasia severity | English | Broca tDCS VS sham | 2 weeks, **2 months** | individualized tDCS treatment enhance aphasia recovery | Randomized Partial Crossover (2 months of interses sion interval) | Level 2 |
| 14 | Meinzer et al., 2016 | Electrical stimulation of the motor cortex enhances treatment outcome in post-stroke aphasia | the effects of intensive language training in combination with M1-tDCS on aphasia impairment and disability parameters | German | M1 A-tDCS VS sham | **6 months** | better results for untrained items in the A-tDCS group | RCT | Level 1b |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 15 | Spielmann et al., 2018 | Transcranial Direct Current Stimulation Does Not Improve Language Outcome in Subacute Post-stroke Aphasia | to investigate the effect of tDCS on word-finding treatment outcome in subacute post stroke aphasia | Dutch | left IFG tDCS VS sham | 10 weeks, **6 months** | results do not support an effect of tDCS as an adjuvant treatment in subacute post stroke aphasia | RCT | Level 1b |
| 16 | Fridriksson et al., 2018 | Transcranial Direct Current Stimulation vs Sham Stimulation to Treat Aphasia After Stroke A Randomized Clinical Trial | to examine the futility of studying A-tDCS as an adjunctive intervention during speech therapy to improve speech production (naming) for chronic post stroke aphasia | English | A-tDCS VS Sham | **4 weeks**, 24 weeks | anodal tDCS during speech therapy is feasible and potentially transformative for aphasia treatment | RCT | Level 1b |

Abbreviations: M1, primary motor cortex; A-tDCS, anodal transcranial direct current stimulation; rTMS, repetitive transcranial magnetic stimulation; IFG, inferior frontal gyrus; LF, low frequency; HF, high frequency; RCT, Randomized controlled trial; PEDro, the Physiotherapy Evidence Database tool.

NOTE: in bold the follow up period that was included into the meta-analysis

**Table 6.1. Summary of the Physiotherapy Evidence Database (PEDro) TMS studies**

| PEDro | Publication | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| NO=0, Yes=1 | Waldowski et al., 2012 RCT | Medina et al., 2012 Randomised Crossover | Barwood et al., 2013 RCT | Seniów et al., 2013 RCT | Khedr et al., 2014 RCT | Tsai et al., 2014 RCT | Wang et al., 2014 RCT | Xue-yan Hu et al., 2018 (1 Hz) RCT |
| 1. eligibility criteria were specified: no yes where: | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 2. subjects were randomly allocated to groups: no yes where: | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 3. allocation was concealed: no yes where: | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 0 |
| 4. the groups were similar at baseline regarding the most important prognostic indicators: no yes where: | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 |
| 5. there was blinding of all subjects no: yes where: | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 |
| 6. there was blinding of all therapists who administered the therapy: no yes where: | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 |
| 7. there was blinding of all assessors who measured at least one key outcome: no yes where: | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 0 |
| 8. measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups: no yes where: | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 9. all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analyzed by "intention to treat": no yes where: | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 10. the results of between-group statistical comparisons are reported for at least one key outcome: no yes where: | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 11. the study provides both point measures and measures of variability for at least one key outcome: no yes where: | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Total | 9 | 9 | 7 | 10 | 10 | 10 | 10 | 6 |

**Table 6.2. Summary of the Physiotherapy Evidence Database (PEDro) tDCS studies**

| PEDro | Publication | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Fiori et al., 2013 (Broca ) | Marangolo et al. 2013 a (Broca ) | Marangolo et al. 2013 b (Broca ) | Polanowska et al., 2013 | Shah-Basak et al., 2015 | Meinzer et al., 2016 | Spielmann et al., 2018 | Fridriksson et al., 2018 |
| | Randomised Crossover | Randomised Crossover | Randomised Crossover | RCT | Randomised Partial Crossover | RCT | RCT | RCT |
| 1. eligibility criteria were specified: no yes where: | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 2. subjects were randomly allocated to groups: no yes where: | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 3. allocation was concealed: no yes where: | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 4. the groups were similar at baseline regarding the most important prognostic indicators: no yes where: | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 5. there was blinding of all subjects: no yes where: | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 6. there was blinding of all therapists who administered the therapy: no yes where: | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 |
| 7. there was blinding of all assessors who measured at least one key outcome: no yes where: | 0 | 0 | 0 | 1 | 0 | 1 | 1 | 0 |
| 8. measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups: no yes where: | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 |
| 9. all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome were analyzed by "intention to treat": no yes where: | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 10. the results of between-group statistical comparisons are reported for at least one key outcome: no yes where: | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| 11. the study provides both point measures and measures of variability for at least one key outcome: no yes where: | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| Total | 6 | 5 | 6 | 8 | 8 | 9 | 9 | 9 |

**Table 7.1. Risk of bias, TMS studies**

| Yes = 1<br>No = 0 | Waldowski et al., 2012 | Medina et al., 2012 | Barwood et al., 2013 | Seniów et al., 2013 | Khedr et al., 2014 | Tsai et al., 2014 | Wang et al., 2014 | Xue-yan Hu et al., 2018 (1 Hz) |
|---|---|---|---|---|---|---|---|---|
| | RCT | Randomized Crossover | RCT | RCT | RCT | RCT | RCT | RCT |
| Was random sequence generation used (i.e. no potential for selection bias)? | 1 | 1 NS[a] | 1 | 1 | 1 | 1 | 1 | 1 NS[a] |
| Was allocation concealment used (i.e. no potential for selection bias)? | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 0 |
| Was there blinding of participants and personnel (i.e. no potential for performance bias)? | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 |
| Was there blinding of outcome assessment (i.e. no potential for detection bias)? | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 |
| Was an objective outcome used? | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Were more than (80%) of participants enrolled in trials included in the analysis? (i.e. no potential attrition bias) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Were data reported consistently for the outcome of interest (i.e. no potential selective reporting)? (no potential reporting bias) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| No other biases reported? (no potential of other bias) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 |
| Did the trials end as scheduled (i.e. not stopped early)? | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| TOTAL | 8 | 8 | 8 | 9 | 9 | 9 | 9 | 5 |

NOTE: [a] randomization was used but the method of randomization is not specified

**Table 7.2. Risk of bias, tDCS studies**

| Yes = 1<br>No = 0 | Fiori et al., 2013 (Broca ) | Marangolo et al. 2013 a (Broca ) | Marangolo et al. 2013 b (Broca ) | Polanowska et al., 2013 | Shah-Basak et al., 2015 | Meinzer et al., 2016 | Spielmann et al., 2018 | Fridriksson et al., 2018 |
|---|---|---|---|---|---|---|---|---|
| | Randomised Crossover | Randomised Crossover | Randomised Crossover | RCT | Randomised Partial Crossover | RCT | RCT | RCT |
| Was random sequence generation used (i.e. no potential for selection bias)? | 1 NS[b] | 1 NS[b] | 1 | 1 NS[b] | 1 NS[b] | 1 | 1 NS[b] | 1 |
| Was allocation concealment used (i.e. no potential for selection bias)? | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Was there blinding of participants and personnel (i.e. no potential for performance bias)? | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 |
| Was there blinding of outcome assessment (i.e. no potential for detection bias)? | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 |
| Was an objective outcome used? | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Were more than (80%) a of participants enrolled in trials included in the analysis? (i.e. no potential attrition bias) | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Were data reported consistently for the outcome of interest (i.e. no potential selective reporting)? (no potential reporting bias) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| No other biases reported? (no potential of other bias) [a] | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 1 |
| Did the trials end as scheduled (i.e. not stopped earlier)? | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| TOTAL | 6 | 5 | 6 | 9 | 4 | 6 | 8 | 7 |

NOTE: [a]. carry over effect in crossover studies; [b] randomization was used but the method of randomization is not specified

**Table 8. Summary of the meta-analysis results**

| Comparison | Number of Studies | Effect Size Summary | 95% CI | Z | p-value for Z | Q - Test for Heterogeneity | p-value for Q | I²: total heterogeneity | Influence Test | Regression Test for Funnel Plot Asymmetry | Rank Correlation Test for Funnel Plot Asymmetry (Kendall's tau) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **tDCS vs. TMS at follow-up** | Test of Moderators: QM(1) = 3.376, p = 0.066 | | | | | | | | | | |
| Overall NIBS Follow up | 16 | 0.53 | 0.2998 , 0.7511 | 4.56 | <.0001 | 17.33 | 0.29 | 24.78% | none | z = 1.3460, p = 0.1783 | tau = 0.1333, p = 0.5056 |
| TMS only Follow-up | 8 | 0.71 | 0.4295 , 0.9966 | 4.92 | <.0001 | 5.94 | 0.55 | 3.54% | Tsai et al., 2014 | z = 0.6874, p = 0.4918 | tau = 0, p = 1.0 |
| tDCS only Follow-up | 8 | 0.33 | 0.0319 , 0.6249 | 2.17 | 0.02 | 7.15 | 0.41 | 18.32% | Spielmann et al., 2018 | z = 0.9908, p = 0.3218 | tau = 0.2857, p = 0.3988 |
| **After vs. Follow-up (Overall NIBS)** | paired t–test: t (14)= -1.15, p = 0.26; 99% CI = [-0.23 , 0.10] | | | | | | | | | | |
| Overall NIBS After | 15 | 0.48 | 0.2623 , 0.7015 | 4.30 | <.0001 | 15.2 | 0.37 | 20.33% | Spielmann et al., 2018 | z = 1.0746, p = 0.2826 | tau = 0.1810, p = 0.3795 |
| **TMS at follow-up vs. TMS immediately after** | paired t–test: t (6)= -0.54, p = 0.24; 99% CI =[ -0.54, 0.24] | | | | | | | | | | |
| TMS only After | 7 | 0.66 | 0.3738 , 0.9450 | 4.52 | <.0001 | 3.16 | 0.79 | 0.00% | none | z = -0.2133, p = 0.8311 | tau = 0.1439, p = 0.7726 |
| **tDCS at follow-up vs. tDCS immediately after** | paired t–test: t (7)= 0.14, p = 0.88; 99% CI = [-0.16 , 0.17] | | | | | | | | | | |
| tDCS only After | 8 | 0.34 | 0.0231 , 0.6522 | 2.1 | 0.0354 | 8.73 | 0.27 | 26.14% | Spielmann et al., 2018 Marangolo et al. 2013 b | z = 1.0851, p = 0.2779 | tau = 0.2857, p = 0.3988 |
| **tDCS vs. TMS RCTs follow-up** | Test of Moderators: QM(1) = 5.616, p = 0.018 | | | | | | | | | | |
| RCTs Overall | 12 | 0.50 | 0.2407 , 0.7512 | 3.81 | p=0.0001 | 15.6 | 0.16 | 33.14% | none | z = 1.3544, p = 0.1756 | tau = 0.2424, p = 0.3108 |
| RCT TMS | 8 | 0.71 | 0.4295 , 0.9966 | 4.93 | <.0001 | 5.94 | 0.55 | 3.54% | Tsai et al., 2014 | z = 0.6874, p = 0.4918 | tau = 0.00, p = 1.0 |
| RCT tDCS | 4 | 0.18 | -0.1556 , 0.5175 | 1.05 | 0.29 | 2.64 | 0.45 | 21.70% | Spielmann et al., 2018 Fridriksson et al., 2018 | z = -0.1602, p = 0.8728 | tau = 0.0000, p = 1.0000 |
| **Chronic: TMS vs. tDCS** | Test of Moderators: QM(1) = 0.203, p= 0.652 | | | | | | | | | | |
| Chronic Overall | 11 | 0.57 | 0.3302 , 0.8143 | 4.163 | <.0001 | 4.74 | 0.90 | 0.00% | none | z = 0.5442, 0.5863 | tau = 0.0545, p = 0.8793 |
| Chronic TMS | 5 | 0.62 | 0.2524 , 0.9884 | 3.30 | 0.001 | 2.71 | 0.60 | 2.54% | Wang et al., 2014 and Tsai et al., 2014 | z = 0.3986, p = 0.6902 | tau = -0.2, p = 0.8167 |
| Chronic tDCS | 6 | 0.54 | 0.2092 , 0.8624 | 3.21 | 0.0013 | 1.92 | 0.8594 | 0.00% | Fridriksson et al., 2018 | z = 0.2920, p = 0.7703 | tau = 0.3333, p = 0.4694 |
| **Subacute** | | | | | | | | | | | |
| Subacute Overall | 5 | 0.48 | -0.0465 , 0.9976 | 1.79 | 0.07 | 11.6 | 0.02 | 65.82% | Khedr et al., 2014 and Spielmann et al., 2018 | z = 3.0079, p = 0.0026 | tau = 0.8000, p = 0.0833 |
| Subacute TMS | 3 | 0.85 | 0.3773 , 1.3215 | 3.53 | 0.0004 | 2.62 | 0.27 | 15.19% | Waldowski et al., 2012 Khedr et al., 2014 | z = 0.7712, p = 0.4406 | tau = 0.3333, p = 1.0000 |

**Table 9. GRADEpro summary**

**Question: Long-term efficacy of transcranial brain stimulation (TMS & tDCS) vs. Control in post-stroke aphasia treatment.**

| Certainty assessment | | | | | | № of patients | | Effect | Certainty |
|---|---|---|---|---|---|---|---|---|---|
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Transcranial brain stimulation** | **Control** | **Absolute (95% CI)** | |
| Long-term efficacy of **tDCS vs. Control** (follow up: range 4 weeks to 24 weeks; Scale from: -1.5 to 2.5) | | | | | | | | | |
| 8 | randomized trials | serious [a] | serious [b] | not serious | not serious | 119 | 132 | SMD **0.33 SD higher** (0.03 higher to 0.6 higher) | ⊕⊕◯◯ LOW |
| Long-term efficacy of **tDCS** vs. Sham **(RCT only)** (follow up: range 4 weeks to 12 weeks; Scale from: -1.5 to 2.5) | | | | | | | | | |
| 4 | randomized trials | not serious | serious [b] | not serious | serious [c] | 88 | 103 | SMD **0.18 SD higher** (0.15 lower to 0.51 higher) | ⊕⊕◯◯ LOW |
| Long-term efficacy of **TMS** vs. Sham **(RCT only)** (follow up: range 8 weeks to 15 weeks; Scale from: -1.5 to 2.5) | | | | | | | | | |
| 8 | randomized trials | not serious | not serious | not serious | not serious | 118 | 99 | SMD **0.71 SD higher** (0.43 higher to 0.996 higher) | ⊕⊕⊕⊕ HIGH |
| Long-term efficacy of **NIBS vs. Control** in patients **with chronic aphasia**. (follow up: range 4 weeks to 24 weeks; Scale from: -1.5 to 2.5) | | | | | | | | | |
| 11 | randomized trials | serious [a] | not serious | not serious | not serious | 145 | 139 | SMD **0.57 SD higher** (0.33 higher to 0.81 higher) | ⊕⊕⊕◯ MODERATE |
| Long-term efficacy of **NIBS vs. Control** in patients with **subacute aphasia**. (follow up: range 4 weeks to 15 weeks; Scale from: -1.5 to 2.5) | | | | | | | | | |
| 5 | randomized trials | not serious | serious [b] | not serious | serious [c] | 92 | 92 | SMD **0.48 SD higher** (0.05 lower to 1.00 higher) | ⊕⊕◯◯ LOW |

**CI:** Confidence interval; **SMD:** Standardized mean difference (Hedges'g)

GRADE Working Group grades of evidence:

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** The authors believe that the true effect is probably close to the estimated effect
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimated effect and could change the estimate.
**Very low quality:** We are very uncertain about the estimate.

**Downgraded Explanations**

[a.] Downgraded as there were serious limitations identified in the risk of bias, since not all the studies were RCTs, same were crossover or open-label studies

[b.] Point estimates vary widely and the direction of the effect was not consistent

[c.] A very small number of included studies