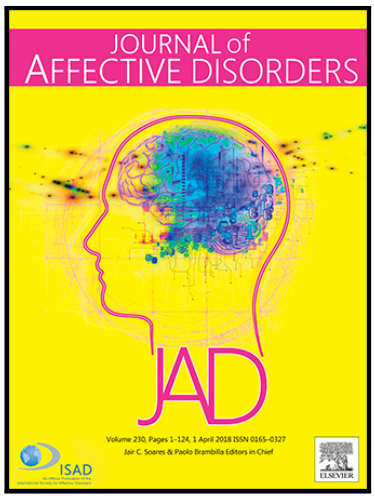

A systematic review of noninvasive brain stimulation for post-stroke depression

Madalina Bucur , Costanza Papagno

PII: S0165-0327(18)30170-8
DOI: 10.1016/j.jad.2018.05.026
Reference: JAD 9802

To appear in: *Journal of Affective Disorders*

Received date: 25 January 2018
Revised date: 9 April 2018
Accepted date: 16 May 2018

Please cite this article as: Madalina Bucur , Costanza Papagno , A systematic review of non-invasive brain stimulation for post-stroke depression, *Journal of Affective Disorders* (2018), doi: 10.1016/j.jad.2018.05.026

Highlights

- We review and discuss the use of NIBS for post-stroke depression
- Both tDCS and TMS can be considered safe or associated with minor side effects
- There is controversial evidence of positive effects of tDCS and TMS in PSD treatment
- New data regarding the stimulation protocol and long-term efficacy are needed

Corresponding author: Madalina Bucur

PhD student

Doctoral School in Cognitive and Brain Sciences

University of Trento

CIMeC - Center for Mind/Brain Sciences

Palazzo Fedrigotti - corso Bettini 31, 38068 Rovereto (TN)

Italy

Phone: +39 328 759 7831

E-mail: madalina.bucur@unitn.it

A systematic review of noninvasive brain stimulation for post-stroke depression

Madalina Bucur[1], Costanza Papagno[1,2]

[1] Center for Mind/Brain Sciences (CIMeC), University of Trento, Italy

[2] Center for Neurocognitive Rehabilitation (CeRiN), Rovereto, Italy

Abstract

Background: Post-stroke depression (PSD) is among the most frequent neuropsychiatric consequences of stroke, negatively affecting the patient's functional recovery and the quality of life. While pharmacological therapy has limited efficacy and important side effects, new appropriate treatments based on specific physiological mechanisms for PSD remain to be developed. Non-invasive brain stimulation (NIBS) techniques, modulating brain plasticity, might offer valid, alternative strategies.

Methods: We systematically searched four databases: MEDLINE, PsycARTICLES, PsycINFO and Web of Science, up to December 2017, using definite keywords, to identify studies on TMS and tDCS treatment for PSD.

Results: Seven studies met the inclusion criteria and the results indicate that both tDCS and rTMS are safe and have very low side effects. The reported positive results, suggesting that these methods can be considered effective therapeutic options, are questionable, and a general statement about their efficacy for PSD is premature due to small sample sizes, heterogeneous methodologies, lack of uniform diagnostic criteria, and divergent data.

Limitations: The selected articles suffer lack of information about quality of life and daily living performance measures; in addition, the number of randomized controlled trials is small.

Conclusion (s): The aim of this review was to analyze current research in the clinical use of noninvasive brain stimulation (NIBS) in PSD treatment in order to verify whether there are alternative perspectives in the treatment of PSD. Given the present evidence, future research is needed to address methodological limitations and evaluate the long-term efficacy of these methods, alone and in combination with pharmacological treatment.

KEYWORDS: post-stroke depression; tDCS; rTMS, noninvasive brain stimulation; stroke

Introduction

Stroke is a cerebrovascular disease considered the leading risk factor for severe physical disability and cognitive impairment (Benjamin et al., 2017; Kelly-Hayes et al., 2003). Even if a significant number of stroke victims achieve at least some spontaneous recovery, it remains one of the main causes of permanent disability (Benjamin et al., 2017). The level of recovery after stroke is mediated by a series of factors like age, gender, education level, stroke type, comorbidities etc. (Kelly-Hayes et al., 2003, Kotila et al., 1984). A serious neuropsychiatric stroke complication, that negatively affects the therapeutic outcome, is post-stroke depression (PSD).

PSD is often described as a depressive syndrome that emerges in the chronological context of stroke (Aben et al., 2001) and is usually noticed in a rather early time period following stroke but also might have a late onset, manifesting itself after more than 6 months (Ayerbe et al., 2013). PSD is considered a form of vascular depression since a "single cerebral infarct may trigger the same pathophysiological changes of depression as slowly evolving vascular ischemia" (Robinson and Jorge, 2015, p222). Even though PSD is not specified in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), the criteria for the diagnosis of PSD match those for Depressive Disorder Due to Another Medical Condition and in the section, Associated Features Supporting Diagnosis, the clear association between depression and stroke is emphasized (American Psychiatric Association, 2013).

Untreated PSD has been associated with decreased treatment efficacy and increased cognitive deficit (Lenzi et al., 2008), significant social impairment, reduced quality of life and high mortality rates (Gainotti et al., 1999; Razmara et al., 2017; Starkstein et al., 2008). Reported rates of PSD range between 11% (House et al., 1991) and 52% (Nys et al., 2005) depending on many factors that differ between studies as regards to assessment tools, setting, time after stroke, lesion characteristics etc. (Aben et al. 2001; Paolucci, 2008; Shi et al., 2017). A recent meta-analysis investigating mood disorders after stroke, based on 108 studies, reported a 33.5% prevalence of all depressive disorders, namely, major

depression accounted for 17.7%, minor depression for 13.1%, and dysthymia for 3.1% (Mitchell et al., 2017). In another study, evaluating depressive symptoms in older stroke survivors, Allan and colleagues (2013) reported three different incidence rates, 36.9, 5.90 and 4.18 episodes per 100 persons year respectively, depending on the instrument chosen to assess depression: (1) major depression following DSM-IV criteria, (2) self-rated Geriatric Depression Scale (GDS) or (3) observer-rated Cornell scale.

Meta-analysis results indicate that the main risk factor for PSD seems to be stroke severity while a valid PSD predictor might be the patients' mental history (Shi et al., 2017). Additionally, studies on risk factors (Rajashekaran et al., 2013; Robinson et al. 1984; Robinson et al. 1986) suggest that left anterior lesions are associated with an increased risk of depression after stroke; namely, the left dorsolateral prefrontal cortex (DLPFC) damage is correlated with more severe depression symptoms (Grajny et al., 2016). Statistics also revealed that depression occurs more frequently in patients after stroke than in the general population and, as most of the mood disorders in psychiatry, the mechanism of PSD has a multifactorial nature, being better explained by a mix of psychological, social, and biological factors (De Ryck et al., 2014).

The treatment of depression after stroke is essential in order to optimize patients' and their relatives' quality of life. Many studies indicate that PSD pharmacological treatments are effective enhancing recovery (Robinson et al., 2015) but others demonstrate a limited efficacy (Baker et al., 2017; Paolucci, 2013) and important side effects (Robinson et al., 2015). For instance, Selective Serotonin Reuptake Inhibitors (SSRIs) usage has been correlated with an increased risk of brain hemorrhage (Hackam and Mrkobrada, 2012). Other studies report some positive impact on depressive symptoms after interventions like ecosystem-focused therapy, life review and problem-solving therapy, music therapy, exercise, behavioral therapy and robotic-assisted neuro-rehabilitation (Baker et al., 2017; Hadidi et al., 2017). Therefore, alternative methods to improve mood have been investigated.

Neuronal reorganization and plasticity that follow stroke may be beneficial or maladaptive and noninvasive brain stimulation techniques (NIBS), like repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), can be used to monitor and modulate this mechanism, facilitating or disrupting the neuronal activity, creating temporary or long-lasting desirable brain changes (Miniussi, 2016), that could improve the PSD treatment making it more effective and less expensive in terms of money and time. For these reasons, rTMS and tDCS have attracted interest as novel methods to treat neurological disorders, including PSD, but their application protocols (e.g., stimulation area, frequency, intensity, polarity, duration) and consequently their effects are characterized by incertitude and great variability. To our knowledge, the only published meta-analysis investigating neuro-stimulation effects in the treatment of PSD is the one by Shen and colleagues (Shen et al., 2017). The authors conclude that rTMS might have beneficial effects on PSD but could not make specific recommendations concerning stimulation parameters or target sites. Unfortunately, their analysis is based exclusively on Chinese studies.

The aim of the present review was to examine the current state of the art on the treatment of PSD with tDCS and TMS and to discuss their efficacy. For this purpose, we selected and analyzed all the published studies, double-blind, randomized placebo-controlled trials (RCTs) but also open-label studies and case reports, paying particular attention to the methods applied, the participants' characteristics and the results.

Methods

We followed previously established methods to perform and report systematic reviews (Liberati et al., 2009; Moher et al., 2015).

Search strategy and selection criteria

The study search was initially kept broad to capture all relevant articles concerning TMS and tDCS treatment interventions for PSD. The following electronic databases were used for papers identification up to December 2017: 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/). Keywords were: (1) “tDCS”, “transcranial direct current stimulation”; “brain stimulation“; “transcranial magnetic stimulation”, “TMS “ AND (2) “post-stroke depression”, “depression after stroke”. All articles retrieved by these search terms were screened for inclusion criteria and, additionally, the reference list of each paper was checked for new, relevant ones.

Titles, abstracts, and full text articles were appraised for eligibility based on the following inclusion criteria: (1) interventions designed for adults with post-stroke depression, (2) non-invasive brain stimulation methods (TMS or tDCS) specified as the main intervention, (3) peer-reviewed, and (4) published in English. Only patients’ studies with an explicit PSD diagnosis, i.e., “mood disorders due to stroke with depressive features, major depressive-like episode, or mixed-mood features” (Robinson and Jorge, 2015, p. 222) were analyzed. All the publications that investigated vascular depression and in which a specific PSD diagnosis was ambiguous because history of stroke was not a compulsory inclusion criterion, were excluded, e.g., Jorge et al. (2008); Narushima et al. (2010). For instance in Narushima et al. (2010) only 8% of 43 patients had a clinical stroke. Crucially, in our review we selected studies of patients with post-stroke depression, i.e. an acute event (PSD), because vascular depression, a chronic cerebrovascular disease, is often associated with cognitive impairment, preventing a clear distinction between depressive and cognitive symptoms (Loganathan et al. 2010). Studies were also excluded if they did not meet one or more of the above conditions or were conference presentations, unpublished data or qualitative articles. Duplicate papers were identified and removed through hand search.

Data extraction and Study quality assessment

Methods characteristics and outcomes were extracted for each included paper. We paid particular attention to participants’ features (sample size, diagnosis and diagnosis instruments, gender, age, post-stroke time interval, pharmacological treatment, lesion type and stroke area), study design, stimulation parameters and brain areas of interest, statistical analysis and reported findings (immediately after treatment and at follow-up); then, we

analyzed similarities and differences between studies with the aim of verifying which parameters are preferable and in which conditions.

Each study design was evaluated and a grade for the level of evidence was assigned according to the modified Sackett Scale, (Sackett et al., 2000) based on Physiotherapy Evidence Database (PEDro) scores (Moseley et al., 2002). The Sackett Scale includes 5 levels of evidence: Level 1 refers to high quality RCTs (PEDro ≥6) and has been divided into level 1a and level 1b, based on the number of RCTs supporting the evidence statement. Level 2 refers to RCTs (PEDro score <6), prospective controlled trials and cohort studies; while for case controls designs (retrospective studies comparing conditions including historical controls) a level 3 is assigned. Level 4 and 5 concern case series, uncontrolled pre-post tests, observational studies, case report designs. The PEDro scale is considered a valid and accepted assessment instrument previously used in systematic reviews (e.g., Marquez et al., 2015; McIntyre et al., 2016; Ownsworth et al., 2016; Zeng et al., 2015). It rates 11 criteria regarding the external and internal validity of the research design (eligibility criteria specification, random allocation, concealed allocation, similarity of groups at baseline, participant blinding, therapist blinding, assessor blinding, < 15% dropout, intention to treat analysis, between-group statistical comparison, and point and variability measures) with a maximum possible score of 10 (the first item, a measure of external validity, is not used for the final score; the items can be scored as either present (1) or absent (0) and the total score is obtained by summation), with a higher score indicating greater quality: 9–10: excellent; 6–8: very good; 4–5: good; < 4: poor (Foley et al., 2003).

Furthermore, in order to assess the entire body of evidence we used the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach to formulate our recommendations about the quality and the strength of evidence. GRADE indicates four levels of evidence along a continuum: high, moderate, low, and very low, taking into consideration different factors like the risk of bias associated to each study, results inconsistency, publication bias etc. (Balshem et al., 2011).

Results

The literature search retrieved 329 articles. Of these, 49 were selected for further evaluation because they were original research articles that explored noninvasive brain stimulation methods (TMS or tDCS) as a possible intervention for PSD. After duplicates removal and full article assessment, seven studies met all inclusion criteria and were further analyzed. Figure 1 shows the search and selection process.

Characteristics of studies

Four experimental studies were therapeutic applications of tDCS (An et al., 2017; Bueno et al., 2011; Valiengo et al., 2016; Valiengo et al., 2017) for the PSD treatment: two experimental research, one case series, and a case report (see Table 1). The remaining three investigated the effects of rTMS (El Etribi et al., 2010; Gu and Chang, 2017; Jorge et al., 2004) on depressed patients after stroke (two were RCTs, see Table 2).

The methodological quality of the 3 RCTs (Gu and Chang, 2017; Jorge et al., 2004; Valiengo et al., 2017) was consistently high, with a mean PEDro score of 8 out of 10 (level 1b evidence). All 3 RCT studies (tDCS and TMS) used randomization; however, the concealed allocation was not specified. Each study used participant blinding and had excellent retention rates. Two studies were non-randomized experimental designs: the El Etribi et al. (2010)'s uncontrolled pre-post study was rated as level 4 evidence while An et al (2017) having a control group was rated as level 3 on the modified Sackett Scale (Sackett et al., 2000). The case series study (Valiengo et al., 2016) and the case report (Bueno et al., 2011) were considered as level 4 and 5 evidence, respectively (see Table 1 and 2). Overall, the level of evidence can be considered low, with only 3 studies out of 7 having a 1b evidence level, while all the others being below level 3.

Participants' characteristics

The review included seven studies involving 157 patients diagnosed with PSD. Regarding the participants' characteristics, there was heterogeneity among studies (Table 3) especially concerning:

(1) the time interval from stroke –not always specified and ranging between 2 years and 6 months;

(2) the PSD diagnosis criteria and the instruments used to assess depressive symptoms - patients were selected on the basis of their scoring above arbitrary cutoff points on depression rating scales (for example: Beck Depression Inventory scores > 12 or > 16, Hamilton Depression Rating Scale scores > 6, Present State Examination modified, Mini-International Neuropsychiatry Interview), and it is important to notice that the effectiveness of these instruments as diagnostic tools was rarely validated;

(3) participants' age ranged between 38 and 71 years,

(4) lesion - the majority of the studies offers only general information about lesion site (left or right hemisphere) and the cause (ischemic or hemorrhagic);

Two studies (Valiengo et al., 2017; El Etribi et al., 2010) report other relevant neurological and psychiatric information like depression type, associated medical conditions and drugs use. With two exceptions (An et al., 2017; Valiengo et al., 2016) all studies report some poor cognitive assessment, e.g. the Mini-Mental State Examination (MMSE), which is totally inappropriate in the case of focal lesions. Only in the case series reported by Valiengo et al. (2016) aphasic patients with PSD were included, while in three papers aphasia was an exclusion criterion (Gu and Chang, 2017; Jorge et al., 2004; Valiengo et al., 2017), and in the other three (An et al., 2017; Bueno et al., 2011; El Etribi et al., 2010), no explicit information was offered about aphasic participants inclusion or exclusion.

Intervention

Target area. In all studies (rTMS and tDCS), the target area was identified in the left DLPFC (F3 according to the International 10-20 EEG System).

Stimulation protocol: rTMS. Two studies (Gu and Chang, 2017; Jorge et al., 2004) used the same stimulation protocol: rTMS was delivered at 110% of the resting motor threshold at a frequency of 10 Hz, 20 trains of 5 seconds duration for 10 sessions (2 consecutive weeks). Instead, in the El Etribi et al.'s (2010) study, an inhibitory rTMS was applied at 100% of the

resting motor threshold at a frequency of 1 Hz for 10 sessions. The magnetic pulses were delivered only with figure of eight shaped coils.

Stimulation protocol: tDCS. Electrode montage, intensity, and duration of tDCS stimulation are important variables that influence the outcome of tDCS studies on PSD recovery, and not only. In all the included studies, tDCS was bi-hemispheric and two equal sized electrodes were used. Each electrode had an area of 25 cm2 (5 cm×5 cm) or in some cases 35 cm2 (5 cm×7cm), with the anode invariable placed over the left and the cathode over the right DLPFC, i.e., located in F3 and F4, respectively, according to the International 10–20 electroencephalography system.

The intensity and duration of the stimulus were homogeneous across studies, tDCS being delivered at an intensity of 2 mA for 30 minutes. The only relevant variation concerned the number of sessions, that ranged between 10 (Bueno et al., 2011) and 20 (An et al., 2017) while in Valiengo's studies (2016, 2017) tDCS was delivered for 10 consecutive workdays, with two additional sessions after two and four weeks, for a total of 12 sessions.

Associated therapies. No other intervention or pharmacological treatment was associated with the stimulation protocol except for three studies. More precisely, tDCS was delivered together with conventional occupational therapy (An et al., 2017) while rTMS was coupled with movement therapy (Gu and Chang, 2017). Only in Bueno's case report (2011), the patient continued a pharmacological treatment; in all the other studies, participants were antidepressant-free.

Placebo. Three studies (Gu and Chang, 2017; Jorge et al., 2004; Valiengo et al., 2017) were double-blind sham-controlled which means that investigators and patients were blinded to the treatment allocations, i.e., the person who performed the stimulation was not informed about the study protocol and someone else did the pre and post-treatment evaluation. In the TMS experiments, the sham condition was performed with the angle of the coil positioned at 90° perpendicular to the skull (Gu and Chang, 2017; Jorge et al., 2004), while in the tDCS experiments the sham condition, which was the same in all studies, implied stopping stimulation after 30 seconds.

Duration. In all the rTMS studies, the treatment lasted for 2 weeks (10 sessions) and focused on relatively short-term follow-up periods ranging between 1 week (Jorge et al., 2004) and 4 weeks (Gu and Chang, 2017). In the tDCS protocols, the duration varied between 4 weeks (20 sessions or 12 sessions) and 2 weeks with 6 months maintenance (Bueno et al., 2011). With the exception of Valiengo et al. (2017) study that included a 2 weeks follow-up period, none of the tDCS treatment evaluated participants in a follow-up.

Outcome measures. Outcome assessment was relatively consistent across studies. Hamilton Depression Rating Scale (HAM-D), the 17 or the 21-item version, was applied in five studies: in one being the only evaluation instrument (El Etribi et al., 2010), in two studies was used together with the Montgomery–Åsberg Depression Rating Scale (MADRS), and in other two with the Beck Depression Inventory (BDI). BDI alone was applied in one research paper (An et al., 2017). Occasionally, these three instruments were used together (Bueno et al., 2011). Other primary efficacy parameters were the response and the remission rates. A good response was defined as a decrease in the Inventory total score so that the patient no longer met the DSM criteria for a depression diagnosis. Remission was defined as a reduction of the scores below a certain point, for example in Jorge et al. (2004) a reduction of Hamilton Depression Rating Scale scores of at least 50% with final HAM-D scores below 8.

Summing up, all the instruments used for the assessment, with the exception of the Aphasic Depression Rating Scale (ADRS) and the Stroke Aphasic Depression Questionnaire (SADQ), in Valiengo et al. (2016), were not specific for the PSD but were rather designed to measure the severity of depression in patients who are otherwise healthy, not taking into consideration many factors that are highly relevant for PSD. Consequently, the assessment based on such instruments was considered inaccurate as extensively discussed in Aben and colleagues' review (2001). To overcome these problematics, new diagnostic tools have been developed, as for example the Structured Assessment of Depression in Brain Damaged Individuals (SADBD) proposed by Gordon et al. in 1991. The authors aimed at designing an

instrument sensitive to depression in a brain-damaged population and, for this purpose, they adapted the items, making them easy to comprehend and simple to answer.

Adverse Effects. Overall, rTMS was well tolerated and only common, mild side effects were reported such as local discomfort at the stimulation site or headache. Severe adverse effects like seizures, hearing impairment or mania were absent. Jorge et al. (2004) described transient headache in six of the 20 participants included in the study, local discomfort at the stimulation site in five patients and an exacerbation of initial insomnia in one patient. Interestingly, they found no significant differences in the adverse events frequency between the active and the sham rTMS groups. El Etribi et al. (2010) reported that 40% of patients complained of headache but easily relieved with paracetamol, while Gu et al. (2017) found no side effects. As concerns tDCS, Bueno et al. (2011) and Valiengo et al. (2016) describe the treatment as well tolerated by all the participants, with the ulterior RCT study Valiengo et al. (2017) reporting no significant difference between the active and the control group.

Results. The first study to explore the effects of NIBS on post-stroke depression was conducted by Jorge et al. (2004). Using a double-blind protocol of active (10 Hz) versus sham rTMS over the left DLPFC in patients with refractory PSD (depression was unresponsive to at least two antidepressants treatments) they reported significant improvement of depressive symptoms after 10 sessions (a reduction of 7.3 points in HAM-D scores). Furthermore, three patients (30%) met criteria for a clinical response and 1 patient (10%) for remission of depression, all from the active rTMS group. Thirteen years later, another double-blind, sham-controlled study, using an identical protocol, confirmed that excitatory rTMS over the left DLPFC could be used to improve PSD symptoms and that this result was maintained for 4 weeks after the end of the treatment (Gu and Chang, 2017). Crucially, in this case, PSD was not refractory, as in the previous research. Another rTMS study (El Etribi et al., 2010) also reported changes in the Ham-D scores compared to the baseline, more precisely a drop of 41.3% that was maintained for over one month in about 60% of the cases. In this study, the authors applied a completely different protocol, namely 10 sessions of inhibitory (1Hz) rTMS at 100% of the rest motor threshold, over the left

DLPFC. In other words, even if the same brain region was stimulated with inhibitory (in one research) and excitatory (in the other two) rTMS, all studies reported positive findings and a reduction of depressive symptoms. At present, the literature does not provide a proper explanation for these incongruent data but it is generally accepted that the effects of rTMS may vary depending on many variables like the brain state at time of stimulation (Perini et al., 2012) or the lesion site, left or right hemisphere.

Three of the four tDCS studies were conducted at the University of São Paulo between 2011 and 2017 (Bueno et al., 2011; Valiengo et al., 2016; Valiengo et al., 2017). Bueno and colleagues (2011) described a 48-year-old patient, who despite being on Fluoxetine for 6 months, was suffering a severe PSD episode. They are the first to report a study in which tDCS is tested as treatment for PSD. After 10 days of 30 minutes anodal tDCS over the left DLPFC and cathodal over the right DLPFC stimulation at a current intensity of 2 mA, the patient showed marked mood and cognitive improvement. A maintenance treatment continued for 6 months (twice a month) and no relapse of symptoms was reported. In 2016, Valiengo et al. also published an open case series (4 cases) that aimed to explore the safety and efficacy of tDCS for the treatment of PSD, but this time, on aphasic patients. The stimulation protocol was very similar to the one presented by Bueno et al. (2011) and all patients exhibited improvement in depression after tDCS. The only RCT study with a tDCS stimulation also belongs to Valiengo and colleagues (2017) and the experimental protocol was similar to the previous ones. As hypothesized, the response rates revealed a higher response level in the active tDCS than in the sham group (37.5% vs 4.1%), while the remission was achieved only in the active tDCS group by 5 (20.8%) patients. Additionally, a significant interaction between the variables time and group was observed: the mean difference at HAM-D 17 scores between active and sham tDCS condition was significant at the end point (6 weeks, i.e. 12 tDCS sessions) but not after 2 weeks (10 tDCS sessions), nor after 4 weeks (12 tDCS sessions). The authors explain these results hypothesizing that tDCS antidepressant effect, similar to the pharmacological treatment, might need more time for maximum manifestation.

An et al. (2017) basically used the same stimulation protocol as the previous ones, but with a different duration, (20 sessions over a period of 4 weeks) and combined conventional occupational therapy with active or sham tDCS. The conclusion was in line with the other studies, confirming that tDCS intervention significantly decreased the depression levels in the experimental group (tDCS and conventional occupational therapy) compared with the control group (sham tDCS and conventional occupational therapy). For instance, the BDI final score change was from 38.8 ± 4.7 (before active tDCS) to 16.8 ± 4.6 (after tDCS), but in this case, the authors did not compare the results from sham vs tDCS. The variable time was also relevant since the depression level of the control group (sham tDCS) also decreased from 39.0 ± 4.6 to 37.8 ± 6.1 but without reaching the statistical significance.

Discussion

PSD is considered a serious and common consequence of acute cerebrovascular accidents (Robinson et al., 2015). Evidence from the literature generally supports the hypothesis that rTMS and tDCS may constitute an effective treatment for depressive symptoms that bypasses the risks associated with antidepressants exposure (Lefaucheur et al., 2014; Shiozawa et al., 2014).

The rationale for the use of TMS and tDCS treatment protocols in PSD is mainly based on two reasons. The first one regards the previous positive results of studies that applied these techniques in depressed patients (without stroke); for instance, the U.S. Food and Drug Administration (FDA) approved rTMS for the treatment of resistant depression since 2008 (Lefaucheur et al., 2014; Padberg et al., 1999; Palm et al. 2016; Pascual-Leone et al., 1996). The second argument is based on the evidence that PSD patients show functional and also structural changes in several cortical regions, as for example, disruption of neural connections among regions regulating mood and cognition, like abnormalities of the cingulate cortex (Ye et al., 2016). In the absence of a pathophysiological hypothesis for PSD, it is not clear if the lessons and results from the depression studies, as for example the fact that TMS has been shown to be safe and effective for resistant depression in the general population (Conelea et al., 2017), should be extended to the PSD treatment,

especially taking into consideration all the neuroplastic mechanisms that characterize the human brain after lesion.

Summing up, all the included studies reported that, following the intervention, the experimental group showed a statistically significant decrease in the depression level, but it is hard to make a comparative analysis between the different studies since nonequivalent parameters were used to establish rTMS and tDCS efficacy. With the exception of Bueno et al. (2011) tDCS for PSD study, that mentioned an important improvement in the daily life activity, as reported by the patient's husband (more active and with less "catastrophic reactions"), none of the other papers provide ecological assessment, limiting the data to standardized scales results and, in some cases (e.g., Jorge et al., 2004; Valiengo et al., 2016) including response and remission rates. Therefore, we cannot say how the change observed in the rating scale translates in the patient's everyday life. Even if the results seem encouraging it is recommended to be very cautious speculating on these findings given the high heterogeneity among studies, the small number of patients, and, especially, the likelihood of publication bias toward positive findings. For example, in a recent research, not included in the review because the participants were not explicitly diagnosed with PSD, the authors find that the delivery of bilaterally rTMS at 10 Hz for 20 minutes did not produce statistically significant changes in the Quick Inventory of Depressive Symptomatology (QIDS) scores (Sasaki et al., 2017). Crucially, the stimulated area was not the DLPFC but a more extended one, the upper-middle of the forehead extending from the external auditory meatus to 30° above the orbitomeatal line.

As previously specified, most intervention descriptions were adequate, but details on treatment procedures and participants' characteristics were missing (e.g. lesion information, the time interval between stroke, depression diagnosis, and treatment onset). Another problem, that makes difficult the comparison between different studies, was represented by the PSD diagnosis criteria. None of the included studies distinguished between major depression and other forms of depressive disorders occurring after the stroke. Also, in order to assess mood disorders and the degree of depressive symptoms, different depression

scales were used, with various and arbitrary cut-off points for the same scale. Another problem concerns the aphasic population that sometimes is explicitly excluded from the studies (e.g., Valiengo et al., 2016) or, in other cases, the cognitive evaluation of language abilities is missing (e.g., El Etribi et al., 2010) even if aphasia is a common stroke consequence, ranging up to one third of the stroke population during the acute phase (Kauhanen et al., 2000). People with aphasia diagnosis or cognitive deficit (Kauhanen et al., 1999) should be included in stroke studies investigating depression and mood disorders, the inclusion criteria, and the instruments to evaluate PDS should be adequate. For instance, there are specific scales to assess PSD, which differ from the traditional ones. Recommended instruments are the Stroke Aphasic Depression Questionnaire-10 (Sutcliffe and Lincoln, 1998), the Stroke Aphasic Depression Questionnaire-H10, the Signs of Depression Scale (van Dijk et al., 2016) and the Structured Assessment of Depression in Brain-Damaged Individuals (SADBD) by Hibbard et al. (1993).

Our initial goal was to compare the relative efficacy between TMS and tDCS and to conduct a meta-analysis using the standardized main differences for the crucial outcomes. Unfortunately, given the limited number of studies and their high heterogeneity (only four studies had a control group, and only three studies directly compared the treatment to the control group), we considered inadequate to perform a quantitative synthesis. Essentially, there are not enough consistent data to make a strong recommendation regarding the effectiveness of rTMS and tDCS (taken together or separately) in improving PSD and consequently, we can formulate only a weak recommendation in favor of the NIBS for PSD. This implies that not all the patients will be best served by such intervention, and in some conditions no improvement could be observed.

The main limitation of the present review concerns the low number of studies and selection biases. For instance, 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 the “gray literature”, i.e., literature that is not formally published in

sources such as books or journal articles" (Higgins et al., 2005, p. 106). An example is the previously mentioned meta-analysis based on Chinese papers (Shen et al., 2017) that found support for rTMS efficiency in PSD treatment. We could not critically evaluate those studies or challenge the reported data because these are published in Chinese and, in addition, we had no access to Chinese journals, but we underline the authors' concern about the heterogeneity, the studies quality, and the potential biases. The same pitfalls were reported in another review, by McIntyre et al. (2016), investigating rTMS for depression among individuals with cerebrovascular disease (including both PSD and vascular depression). In spite of the encouraging results, that seemed to indicate some effectiveness of rTMS, they could not formulate a univocal conclusion based on the available data.

Considering the current findings, we cannot support the efficacy of a specific stimulation protocol, or indicate which stimulation technique is recommended, and for what type of patients. It can be speculated that rTMS could be more effective for refractory PSD (Jorge et al., 2004), while tDCS being considered "easy" to apply, more flexible and less expensive could be a better choice in other cases. There seem to be two main theoretical hypotheses to choose a certain stimulation protocol for PSD treatment. rTMS studies rather assume the so-called hypofrontality hypothesis (Galynker et al., 1998) targeting only the left DLPFC but many parameters as the stimulation frequency and duration are still unclear. Conversely, in the tDCS studies a bihemispheric montage was used, anodal over the left and cathodal over the right DLPFC, a choice that might be based on an interhemispheric frontal imbalance hypothesis (Debener et al., 2000; Reid et al., 1998). Concerning the positioning of the reference electrode, there is no current evidence that F4 positioning is preferable to the supraorbital positioning. For instance, in the evidence-based guidelines on the therapeutic use of tDCS, Lefaucheur and colleagues data indicate that anodal stimulation of the left DLPFC with right orbitofrontal cathode is "probably effective in patients with no drug-resistant major depressive episode (Level B) and probably ineffective in patients with drug-resistant major depressive episode (Level B) "(Lefaucheur et al., 2017, p 75). However, these are recommendations for depressed persons without stroke.

With reference to safety, both rTMS and tDCS are generally considered safe if the appropriate guidelines and recommendations are followed, e.g. Rossi and colleagues (2009) for TMS, and Nitsche et al. (2003), Woods et al. (2016) for tDCS. Even though none of the considered studies reported any adverse events, more research is needed to verify the safety parameters in specific subgroups like post-stroke patients because the intensity and location of current flow might differ due to changes in the local anatomy and lesion time evolution. An important challenge for future research will be to collect unequivocal data about tolerability, stimulation parameters, and neuroplasticity changes of tDCS and rTMS in larger RCTs involving PSD patients.

Except for a case study report (Bueno et al., 2011), all studies investigated tDCS and TMS as a mono-therapy in medication-free patients. Concomitant pharmacotherapy can influence neuroplasticity effects of rTMS and tDCS; for example, mood stabilizers seem to nullify tDCS-elicited excitability changes (Palm et al., 2016), while in a study of Brunoni and colleagues (Brunoni et al., 2013) on depressed patients, the combined sertraline and tDCS treatment was more effective than sertraline or tDCS alone. Following this tendency, possibly the best intervention for PSD will be to incorporate different approaches in order to maximize the neuronal plasticity.

The future important challenges will be to collect clear evidence for the long-term efficacy of these methods and to investigate the potentiation of TMS and tDCS-elicited neuroplasticity changes by pharmacological therapies. The combined therapy could be a promising asset towards a quicker and more sustained improvement of depressive disorders (Palm et al., 2016). Important returns could be expected. First, the positive cost-benefit ratio of tDCS could reduce treatment costs. Patients or relatives could learn to apply stimulation at home with personalized protocols (Palm et al., 2016), but the objective should be related to the neuropsychological profile and the individual goals.

Acknowledgements: This research was supported by the Center for Mind/Brain Sciences and University of Trento and by PhD program sponsors: the Autonomous Province

of Trento, the Fondazione Cassa di Risparmio di Trento e Rovereto and the Municipality of Trento.

Conflicts of Interest

Manuscript title: A systematic review of noninvasive brain stimulation for post-stroke depression.

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Author names: Madalina Bucur [1], Costanza Papagno[1,2]

[1] Center for Mind/Brain Sciences (CIMeC), University of Trento, Italy

[2] Center for Neurocognitive Rehabilitation (CeRiN), Italy

References

1. Aben, I., Verhey, F., Honig, A., Lodder, J., Lousberg, R. and Maes, M., 2001. Research into the specificity of depression after stroke: a review on an unresolved issue. Prog. Neuropsychopharmacol. Biol. Psychiatry. 25, 671-89.

2. Allan, L.M., Rowan, E.N., Thomas, A.J., Polvikoski, T.M., O'Brien, J.T. and Kalaria, R.N., 2013. Long-term incidence of depression and predictors of depressive symptoms in older stroke survivors. Br J Psychiatry. 203, 453-460.

3. American Psychiatric Association, 2013. Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub.

4. An, T.G., Kim, S.H. and Kim, K.U., 2017. Effect of transcranial direct current stimulation of stroke patients on depression and quality of life. J. Phys. Ther. Sci. 29, 505-507.

5. Ayerbe, L., Ayis, S., Wolfe, C.D. and Rudd, A.G., 2013. Natural history, predictors and outcomes of depression after stroke: systematic review and meta-analysis. Br. J. Psychiatry. 202, 14-21.

6. Baker, C., Worrall, L., Rose, M., Hudson, K., Ryan, B. and O'Byrne, L., 2017. A systematic review of rehabilitation interventions to prevent and treat depression in post-stroke aphasia. Disabil. Rehabil. 1-23.

7. Balshem, H., Helfand, M., Schünemann, H.J., Oxman, A.D., Kunz, R., Brozek, J., Vist, G.E., Falck-Ytter, Y., Meerpohl, J., Norris, S. and Guyatt, G.H., 2011. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 64, 401-406.

8. Benjamin, E.J., Blaha, M.J., Chiuve, S.E., Cushman, M., Das, S.R., Deo, R., de Ferranti, S.D., Floyd, J., Fornage, M., Gillespie, C. and Isasi, C.R., 2017. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. Circulation 135, e146-e603.

9. Bueno, V.F., Brunoni, A.R., Boggio, P.S., Bensenor, I.M. and Fregni, F., 2011. Mood and cognitive effects of transcranial direct current stimulation in post-stroke depression. Neurocase. 17, 318-322.

10. Brunoni, A.R., Valiengo, L., Baccaro, A., Zanão, T.A., de Oliveira, J.F., Goulart, A., Boggio, P.S., Lotufo, P.A., Benseñor, I.M. and Fregni, F., 2013. The sertraline vs electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. JAMA psychiatry. 70, 383-391.

11. Conelea, C.A., Philip, N.S., Yip, A.G., Barnes, J.L., Niedzwiecki, M.J., Greenberg, B.D., Tyrka, A.R. and Carpenter, L.L., 2017. Transcranial magnetic stimulation for treatment-resistant depression: Naturalistic treatment outcomes for younger versus older patients. J. Affect. Disord. 217, 42-47.

12. Debener, S., Beauducel, A., Nessler, D., Brocke, B., Heilemann, H. and Kayser, J., 2000. Is resting anterior EEG alpha asymmetry a trait marker for depression? Neuropsychobiology. 41, 31-37.

13. De Ryck, A., Fransen, E., Brouns, R., Geurden, M., Peij, D., Mariën, P., De Deyn, P.P. and Engelborghs, S., 2014. Poststroke depression and its multifactorial nature: results from a prospective longitudinal study. J. Neurol. Sci. 347, 159-166.

14. El Etribi, A., El Nahas, N., Nagy, N. and Nabil, H., 2010. Repetitive transcranial magnetic stimulation treatment in post stroke depression.Curr. Psychiatry. 17, 9-14.

15. Foley, N. C., Teasell, R. W., Bhogal, S. K., & Speechley, M. R., 2003. Stroke rehabilitation evidence-based review: methodology. Top Stroke Rehabil. 10, 1-7.

16. Gainotti, G., Azzoni, A. and Marra, C., 1999. Frequency, phenomenology and anatomical-clinical correlates of major post-stroke depression. Br. J. Psychiatry.175, 163-167.

17. Galynker, I.I., Cai, J., Ongseng, F. and Finestone, H., 1998. Hypofrontality and negative symptoms in major depressive disorder. J. Nucl. Med. 39, p.608.

18. Gordon, W.A., Hibbard, M.R., Egelko, S., Riley, E., Simon, D., Diller, L., Ross, E.D. and Lieberman, A., 1991. Issues in the diagnosis of post-stroke depression. Rehabil. Psychol. 36, p.71.

19. Grajny, K., Pyata, H., Spiegel, K., Lacey, E.H., Xing, S., Brophy, C. and Turkeltaub, P.E., 2016. Depression symptoms in chronic left hemisphere stroke are related to dorsolateral prefrontal cortex damage. J. Neuropsychiatry Clin. Neurosci. 28, 292-298.

20. Gu, S.Y. and Chang, M.C., 2017. The Effects of 10-Hz Repetitive Transcranial Magnetic Stimulation on Depression in Chronic Stroke Patients. Brain. Stimul. 10, 270-274.

21. Hackam, D.G. and Mrkobrada, M., 2012. Selective serotonin reuptake inhibitors and brain hemorrhage A meta-analysis. Neurology. 79, 1862-1865.

22. Hadidi, N.N., Wagner, R.L.H. and Lindquist, R., 2017. Nonpharmacological Treatments for Post-Stroke Depression: An Integrative Review of the Literature. Res. Gerontol. Nurs. 10, 182-195.

23. Hibbard, M.R., Stein, P.N., Gordon, W.A. and Sliwinksi, M., 1993. The Structured Assessment of Depression in Brain-Damaged Individuals: Administration and scoring manual. Mount Sinai Medical Center, Department of Rehabilitation Medicine, New York.

24. Higgins, J.P. and Green, S., 2005. Cochrane handbook for systematic reviews of interventions.

25. House, A., Dennis, M., Mogridge, L., Warlow, C., Hawton, K. and Jones, L., 1991. Mood disorders in the year after first stroke. Br. J. Psychiatry. 158, 83-92.

26. Jorge, R.E., Moser, D.J., Acion, L. and Robinson, R.G., 2008. Treatment of vascular depression using repetitive transcranial magnetic stimulation. Arch Gen Psychiatry. 65, 268-276.

27. Jorge, R.E., Robinson, R.G., Tateno, A., Narushima, K., Acion, L., Moser, D., Arndt, S. and Chemerinski, E., 2004. Repetitive transcranial magnetic stimulation as treatment of poststroke depression: a preliminary study. Biol. Psychiatry. 55, 398-405.

28. Kauhanen, M.L., Korpelainen, J.T., Hiltunen, P., Brusin, E., Mononen, H., Määttä, R., Nieminen, P., Sotaniemi, K.A. and Myllylä, V.V., 1999. Poststroke depression correlates with cognitive impairment and neurological deficits. Stroke. 30, 1875-1880.

29. Kauhanen, M.L., Korpelainen, J.T., Hiltunen, P., Määttä, R., Mononen, H., Brusin, E., Sotaniemi, K.A. and Myllylä, V.V., 2000. Aphasia, depression, and non-verbal cognitive impairment in ischaemic stroke. Cerebrovasc. Dis. 10, 455-461.

30. Kelly-Hayes, M., Beiser, A., Kase, C.S., Scaramucci, A., D'Agostino, R.B. and Wolf, P.A., 2003. The influence of gender and age on disability following ischemic stroke: the Framingham study. J. Stroke Cerebrovasc. Dis. 12, 119-26.

31. Kotila, M., Waltimo, O., Niemi, M.L., Laaksonen, R.I.T.V.A. and Lempinen, M., 1984. The profile of recovery from stroke and factors influencing outcome. Stroke. 15, 1039-1044.

32. Lefaucheur, J.P., André-Obadia, N., Antal, A., Ayache, S.S., Baeken, C., Benninger, D.H., Cantello, R.M., Cincotta, M., de Carvalho, M., De Ridder, D. and Devanne, H., 2014. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin. Neurophysiol. 125, 2150-2206.

33. Lefaucheur, J.P., Antal, A., Ayache, S.S., Benninger, D.H., Brunelin, J., Cogiamanian, F., Cotelli, M., De Ridder, D., Ferrucci, R., Langguth, B. and Marangolo, P., 2017. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clin. Neurophysiol. 128, 56-92.

34. Lenzi, G.L., Altieri, M. and Maestrini, I., 2008. Post-stroke depression. Rev. Neurol. (Paris). 164, 837-40.

35. Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gøtzsche, P.C., Ioannidis, J.P., Clarke, M., Devereaux, P.J., Kleijnen, J. and Moher, D., 2009. The PRISMA

statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 6, e1000100.

36. Loganathan, S., Phutane, V.H., Prakash, O. and Varghese, M., 2010. Progression of vascular depression to possible vascular dementia. J Neuropsychiatry Clin Neurosci. 22,.451-e34.

37. Marquez, J., Vliet, P., McElduff, P., Lagopoulos, J., & Parsons, M., 2015. Transcranial direct current stimulation (tDCS): does it have merit in stroke rehabilitation? A systematic review. Int J Stroke. 10, 306-316.

38. McIntyre, A., Thompson, S., Burhan, A., Mehta, S. and Teasell, R., 2016. Repetitive transcranial magnetic stimulation for depression due to cerebrovascular disease: a systematic review. J Stroke Cerebrovasc Dis. 25, 2792-2800.

39. Miniussi, C., 2016. A Foreword on the Use of Noninvasive Brain Stimulation in Psychology. Eur. Psychol. 21, 1-3.

40. Mitchell, A.J., Sheth, B., Gill, J., Yadegarfar, M., Stubbs, B., Yadegarfar, M. and Meader, N., 2017. Prevalence and predictors of post-stroke mood disorders: A meta-analysis and meta-regression of depression, anxiety and adjustment disorder. Gen Hosp Psychiatry. 47, 48-60.

41. Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P. and Stewart, L.A., 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst. Rev. 4, p.1.

42. Moseley AM, Herbert RD, Sherrington C, et al., 2002. Evidence for physiotherapy practice: a survey of the Physiotherapy Evidence Database (PEDro). Aust J Physiother. 48, 43- 49.

43. Narushima, K., McCormick, L.M., Yamada, T., Thatcher, R.W. and Robinson, R.G., 2010. Subgenual cingulate theta activity predicts treatment response of repetitive transcranial magnetic stimulation in participants with vascular depression. J Neuropsychiatry Clin Neurosci. 22, 75-84.

44. Nitsche, M.A., Liebetanz, D., Lang, N., Antal, A., Tergau, F. and Paulus, W., 2003. Safety criteria for transcranial direct current stimulation (tDCS) in humans. Clin. Neurophysiol. 114, 2220-2222.

45. Nys, G.M.S., Van Zandvoort, M.J.E., Van der Worp, H.B., De Haan, E.H.F., De Kort, P.L.M. and Kappelle, L.J., 2005. Early depressive symptoms after stroke: neuropsychological correlates and lesion characteristics. J. Neurol. Sci. 228, 27-33.

46. Ownsworth, T., & Haslam, C., 2016. Impact of rehabilitation on self-concept following traumatic brain injury: An exploratory systematic review of intervention methodology and efficacy. Neuropsychol Rehabil. 26, 1-35.

47. Padberg, F., Zwanzger, P., Thoma, H., Kathmann, N., Haag, C., Greenberg, B.D., Hampel, H. and Möller, H.J., 1999. Repetitive transcranial magnetic stimulation (rTMS) in pharmacotherapy-refractory major depression: comparative study of fast, slow and sham rTMS. Psychiatry Res. 88, 163-171.

48. Palm, U., Hasan, A., Strube, W. and Padberg, F., 2016. tDCS for the treatment of depression: a comprehensive review. Eur. Arch. Psychiatry. Clin. Neurosci. 266, 681-694.

49. Paolucci, S., 2008. Epidemiology and treatment of post-stroke depression. Neuropsychiatr Dis Treat. 4, 145.

50. Paolucci, S., 2013. Role, indications, and controversies of antidepressant therapy in chronic stroke patients. Eur. J. Phys. Rehabil. Med. 49, 233-241.

51. Pascual-Leone, A., Rubio, B., Pallardó, F. and Catalá, M.D., 1996. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. The Lancet. 348, 233-237.

52. Perini, F., Cattaneo, L., Carrasco, M. and Schwarzbach, J.V., 2012. Occipital transcranial magnetic stimulation has an activity-dependent suppressive effect. J. Neurosci. 32, 12361-12365.

53. Razmara, A., Valle, N., Markovic, D., Sanossian, N., Ovbiagele, B., Dutta, T., Towfighi, A., 2017. Depression Is Associated with a Higher Risk of Death among Stroke Survivors. J Stroke Cerebrovasc Dis. 26, 2870-2879.

54. Rajashekaran, P., Pai, K., Thunga, R. and Unnikrishnan, B., 2013. Post-stroke depression and lesion location: A hospital based cross-sectional study. Indian J. Psychiatry. 55, 343.

55. Reid, S. A., Duke, L. M., & Allen, J. J., 1998. Resting frontal electroencephalographic asymmetry in depression: Inconsistencies suggest the need to identify mediating factors. Psychophysiology. 35, 389-404.

56. Robinson, R.G. and Jorge, R.E., 2015. Post-stroke depression: a review. Am. J. Psychiatry. 173, 221-31.

57. Robinson, R.G., Kubos, K.L., Starr, L.B., Rao, K. and Price, T.R., 1984. Mood disorders in stroke patients: importance of location of lesion. Brain. 107, 81-93.

58. Robinson, R.G., Lipsey, J.R., Rao, K. and Price, T.R., 1986. Two-year longitudinal study of post-stroke mood disorders: comparison of acute-onset with delayed-onset depression. Am. J. Psychiatry. 143, 1238-1244.

59. Rossi, S., Hallett, M., Rossini, P.M., Pascual-Leone, A. and Safety of TMS Consensus Group, 2009. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin. Neurophysiol. 120, 2008-2039.

60. Sasaki, N., Hara, T., Yamada, N., Niimi, M., Kakuda, W. and Abo, M., 2017. The Efficacy of High-Frequency Repetitive Transcranial Magnetic Stimulation for Improving Apathy in Chronic Stroke Patients. Eur. Neurol. Rev. 78, 28-32.

61. Sackett, D.L., Straus, S.E., Richardson, W.S., Rosenberg, W., & Haynes, R.B. , 2000. Evidence-Based Medicine: How to Practice and Teach EBM (2nd ed.). Edinburgh: Churchill Livingstone.

62. Shen, X., Liu, M., Cheng, Y., Jia, C., Pan, X., Gou, Q., Liu, X., Cao, H. and Zhang, L., 2017. Repetitive transcranial magnetic stimulation for the treatment of post-stroke depression: A systematic review and meta-analysis of randomized controlled clinical trials. J. Affect. Disord. 211, 65–74.

63. Shi, Y., Yang, D., Zeng, Y. and Wu, W., 2017. Risk Factors for Post-stroke Depression: A Meta-analysis. Front. Aging Neurosci. 9, 218.

64. Shiozawa, P., Fregni, F., Benseñor, I.M., Lotufo, P.A., Berlim, M.T., Daskalakis, J.Z., Cordeiro, Q. and Brunoni, A.R., 2014. Transcranial direct current stimulation for major depression: an updated systematic review and meta-analysis. Int. J. Neuropsychopharmacol. 17, 1443-1452.

65. Starkstein, S.E., Mizrahi, R. and Power, B.D., 2008. Antidepressant therapy in post-stroke depression. Expert. Opin. Pharmacother. 9, 1291-8.

66. Sutcliffe, L.M. and Lincoln, N.B., 1998. The assessment of depression in aphasic stroke patients: the development of the Stroke Aphasic Depression Questionnaire. Clinical rehabilitation, 12(6), pp.506-513.

67. Valiengo, L.C., Casati, R., Bolognini, N., Lotufo, P.A., Benseñor, I.M., Goulart, A.C. and Brunoni, A.R., 2016. Transcranial direct current stimulation for the treatment of post-stroke depression in aphasic patients: a case series. Neurocase. 22, 225-228.

68. Valiengo, L.C., Goulart, A.C., de Oliveira, J.F., Benseñor, I.M., Lotufo, P.A. and Brunoni, A.R., 2017. Transcranial direct current stimulation for the treatment of post-stroke depression: results from a randomised, sham-controlled, double-blinded trial. J. Neurol. Neurosurg. Psychiatry. 88, 170-175.

69. van Dijk, M.J., de Man-van Ginkel, J.M., Hafsteinsdóttir, T.B. and Schuurmans, M.J., 2016. Identifying depression post-stroke in patients with aphasia: a systematic review of the reliability, validity and feasibility of available instruments. Clin. Rehabil. 30, 795-810.

70. Woods, A.J., Antal, A., Bikson, M., Boggio, P.S., Brunoni, A.R., Celnik, P., Cohen, L.G., Fregni, F., Herrmann, C.S., Kappenman, E.S. and Knotkova, H., 2016. A technical guide to tDCS, and related non-invasive brain stimulation tools. Clin. Neurophysiol. 127, 1031-1048.

71. Ye, C., Wu, J., Chen, X., Zhang, C., Li, H., Mao, S. and Ma, H.T., 2016, August. Structural changes of cingulate cortex in post stroke depression. In Engineering in Medicine and Biology Society (EMBC), 2016. 38th Annual International Conference.

72. Zeng, X., Zhang, Y., Kwong, J. S., Zhang, C., Li, S., Sun, F., ... & Du, L. , 2015. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. Int J Evid Based Healthc. 8, 2-10.

Figure 1. Flow Diagram of study selection and inclusion.

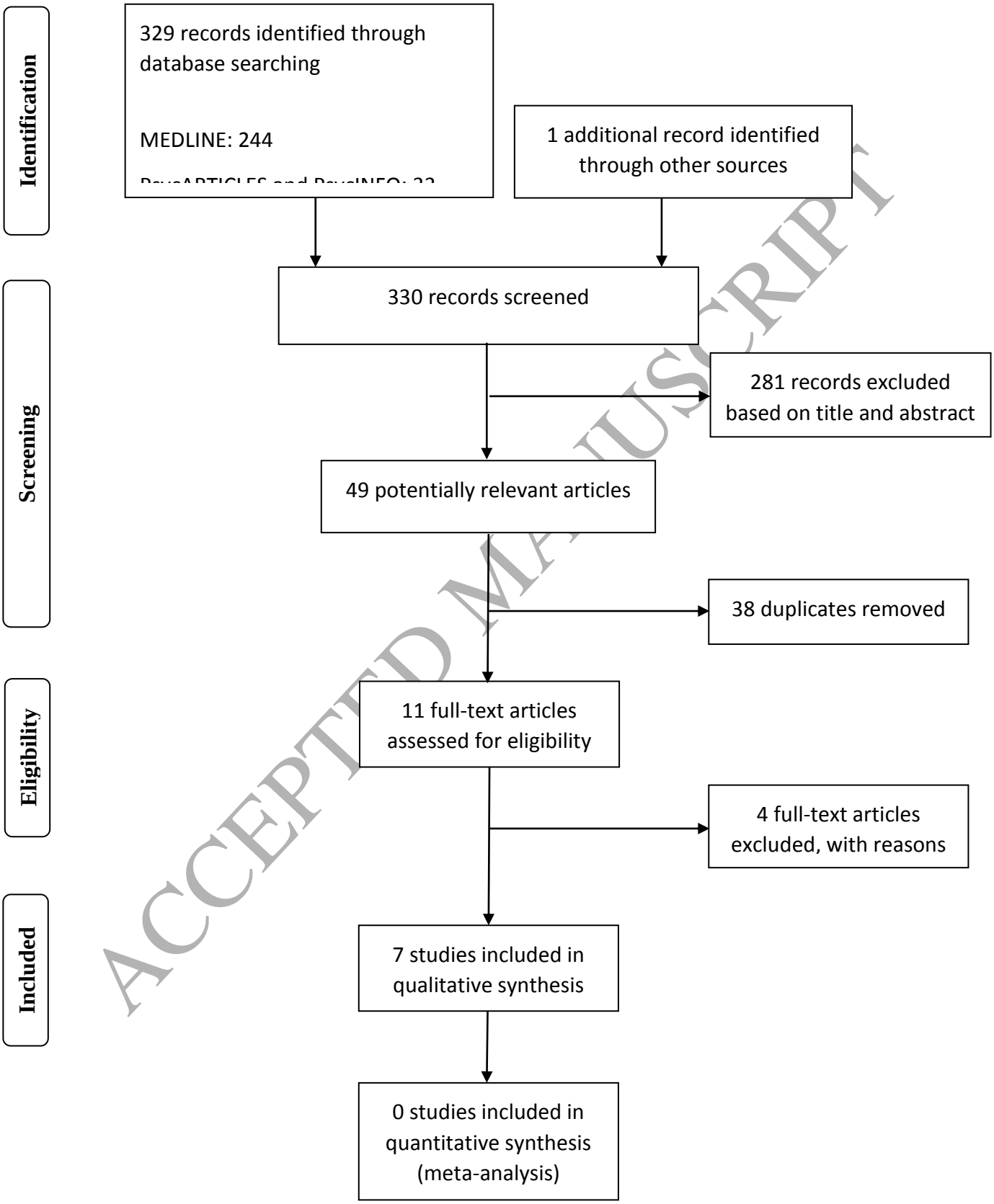

Table 1 Summary of tDCS study characteristics

Study	Study design	tDCS montage		Current intensity	Number of stimulations Duration	Analysis	Sham	Primary Outcome	Results / Authors conclusions	Follow-up	Evidence (PEDro)
		Electrode position	**Reference electrode**								**Modified Sackett Scale**
An et al., 2017 (4)	Experimental research, sham-controlled	Anode left DLPFC	Cathode right DLPFC	2 mA	20 sessions of 30 min. (4 weeks)	*pre VS post tDCS *sham VS active	the stimulation was stopped 30 seconds after the application	BDI	TDCS intervention caused a significant decrease in depression levels in the experimental group.	No Follow-up.	**Level 3**
Valiengo et al., 2017 (68)	Experimental research, (RCT) Double-blind, sham-controlled	Anode left DLPFC	Cathode right DLPFC	2 mA	12 sessions of 30 min. 2 weeks x 10sessions, 2 weeks x 2 sessions	*baseline 2nd, 4th ,6th week *sham VS active	the stimulation was stopped 30 seconds after the application	HAM-D17 Response Remission	Active tDCS was significantly superior to sham at end point	2 weeks	**Level 1b**
Valiengo, et al., 2016 (67)	Case study Open case series	Anode left DLPFC	Cathode right DLPFC	2 mA	12 sessions of 30 min. 2 weeks x 10sessions, 2 weeks x 2 sessions	*Baseline, 2nd, 4th,6th Week	No sham	ADRS SADQ	All 4 patients exhibited improvement in depression after tDCS	No Follow-up	**Level 4**
Bueno, et al., 2011 (9)	Case study	Anode left DLPFC	Cathode right DLPFC	2 mA	10 sessions of 30 min. maintenance for 6 months (twice a	*Baseline, 2nd Week, 6 Months	No sham	HAM-D BDI MADRS	Marked improvement in the depressive symptoms.	No Follow-up	**Level 5**

month)

Abbreviations: tDCS, Transcranial direct current stimulation; DLPFC, dorsolateral prefrontal cortex; RCT, Randomized controlled trial; BDI, Beck Depression Inventory; HAM-D, Hamilton Depression Rating Scale; ADRS, Aphasic Depression Rating Scale; SADQ, Stroke Aphasic Depression Questionnaire; MADRS , Montgomery-Asberg Depression Rating Scale; PEDro, the Physiotherapy Evidence Database tool.

Table 2 Summary of TMS study characteristics

Study	Study design	Target area(s)	rTMS Frequency	Intensity (% MT)	Trains of session Number of sessions	Sham	Treatment protocol and Analysis	Outcome measure	Results / Authors conclusions	Follow-up	Evidence (PEDro)
Gu, et al., 2017 (20)	Experimental research, (RCT) Double-blind, sham-controlled	left DLPFC	10 HZ	110 %	20 trains of 5 seconds, 10 sessions (10000 pulses) (2 weeks)	angle of the coil at 90° perpendicular to the skull	*4 weeks, 1 day pre *1 day, 4 weeks post *sham VS active rTMS	BDI HAM-D17	BDI and HAM-D17were significantly decreased at 1 day and 4 weeks after treatment in the rTMS group compared to the sham	4 weeks	**Level 1b**
El Etribi et al.,2010 (14)	Experimental research	left DLPFC	1 HZ	100 %	10 trains of 10 seconds 10 session (1000 pulses) (2 weeks)	No sham	*Baseline, 2nd ,4th, 6th Week	HAM-D21	About 60% of the patients showed drop of at least 41.3 % from the baseline in scores on the HAM-D21 and clinical improvement.	2 and 4 weeks	**Level 4**
Jorge, et al, 2004 (27)	Experimental research, (RCT) Double-blind, sham-controll	left DLPFC	10 HZ	110 %	20 trains of 5 seconds, 10 sessions (100	angle of the coil at 90° perpendicular to the skull	*Baseline, 2nd and 3rd Week *sham VS active	HAM-D17 Response Remission	Was found a significant difference between the active	1 week	**Level 1b**

ed	00 pulse s) (2 week s)	rTMS	and the sham rTMS, active group showed a mean reductio n of 7.3 points in HAM-D17 scores.

Abbreviations: rTMS, repetitive transcranial magnetic stimulation; MT, the motor threshold; DLPFC, dorsolateral prefrontal cortex; RCT, Randomized controlled trial; BDI, Beck Depression Inventory; HAM-D17, 17-item version of the Hamilton Depression Rating Scale; HAM-D21, 21-item version of the Hamilton Depression Rating Scale; PEDro, the Physiotherapy Evidence Database tool.

Table 3 Summary of the participant's characteristics

Study	Sample	Diagnosis and diagnosis instruments	Experimental group characteristics						Medication
			Male	Female	Mean Age (SD)	Mean Stroke Interval (months)	Treatment	Lesion type and Hemisphere	
An TG et al., 2017 (4)	40 20 control group 20 experimental	PSD * BDI scores >16	17	3	51.0 ± 11.7	14.6 ± 6.3	conventional occupational therapy + tDCS	11 cerebral infarction 9 hemorrhage 7 right hemisphere 13 left hemisphere	not specified
Valiengo et al., 2017 (68)	48 (5 drop-outs) 24 control group 24 experimental	PSD * MINI	12	12	62.2 ± 12.3	11.1 ± 2	tDCS	11 right side (stroke) 10 subcortical structures (stroke) 8 frontal injury (stroke)	antidepressant-free
Valiengo et al., 2016 (67)	4	PSD (confirmed by a psychiatrist) with Broca's aphasia diagnosis	0	4	48.2 ± 11.6	6 ± 4.08	tDCS	stroke type: 3 ischemic 1 hemorrhage Hemisphere not specified	antidepressant-free
Bueno, V. F. et al., 2011 (9)	a 48-year-old woman	PSD * MINI	0	1	48	not specified	tDCS	ischemic stroke: left basal ganglia and left insula	Fluoxetine 40 mg/day for 6 months
Gu, S. Y. et al., 2017 (20)	24 12 control group 12 experimental	PSD * BDI scores >12 * HAM-D17 scores >6	6	6	58.1± 8.7	10.3 ± 2.7	movement therapy + rTMS	stroke type: 11 infarct 9 hemorrhage Hemisphere not specified	not specified
El Etribi et al., 2010 (14)	20 experimental	PSD * K-SADS * SCID for DSM-IV	12	8	51.9 ± 4.77	not specified	rTMS	Stroke 10 left hemisphere 10 right hemisphere	antidepressant-free

Jorge, R. E. et al., 2004 (27)	20 10 control group 10 experimental	PSD * PSE according to DSM- VI *unresponsive to at least two treatments with antidepressants	6	4	63.1 ± 8.1	not specified	rTMS	3 Cortico-Subcortical Strokes 6 Deep Hemispheric WM and GM 1 Brainstem/Cerebellar Strokes Hemisphere not specified	antidepressant-free

Abbreviations: SD, standard deviation; PSD, post-stroke depression; BDI, Beck Depression Inventory; tDCS, Transcranial direct current stimulation; MINI, Mini-International Neuropsychiatry Interview; HAM-D17, 17-item version of the Hamilton Depression Rating Scale; rTMS, repetitive transcranial magnetic stimulation, K-SADS, Schedule for Affective Disorders and Schizophrenia; SCID, Structured Clinical Interview for DSM-IV; DSM-IV, Diagnostic and Statistical Manual Fourth Edition; PSE, Present State Examination