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Non-invasive brain stimulations for unilateral spatial neglect after stroke: a systematic review and meta-analysis of randomized and non-randomized controlled trials

Dissertação apresentada à Faculdade de Medicina, Universidade Estadual Paulista "Júlio de Mesquita Filho", Câmpus de Botucatu, para obtenção do título de Mestre em Clínica Médica.

Orientador: Prof. Dr. RODRIGO BAZAN

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Palavras-chave: Acidente Vascular Cerebral; Cérebro; Estimulação; Não-invasiva; Negligência.

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RESUMO

Objetivo: Uma revisão sistemática para investigar o impacto da estimulação cerebral não-invasivas (i.e., estimulação transcraniana de corrente direta (ETCC), estimulação magnética transcraniana repetitiva (EMTr) e Theta-Burst (TBS)) em comparação com placebo para negligência espacial unilateral após acidente vascular encefálico (NEU).

Bases de dados: Pesquisas na MEDLINE, EMBASE, CENTRAL, CINAHL e LILACS até julho de 2017.

Seleção de estudos: Ensaios controlados randomizados (ECRs) e não-ECRs.

Extração de dados: Dois pares de revisores examinaram de forma independente artigos potencialmente elegíveis, extraíram dados dos estudos incluídos sobre populações, intervenções e resultados e avaliaram seu risco de viés. Utilizamos a abordagem GRADE para avaliar a certeza geral da evidência por resultado.

Síntese de dados: 12 ensaios randomizados, incluindo 273 participantes, e quatro não-ECRs, incluindo 94 participantes, mostraram ser elegíveis. Os resultados fornecidos pelos ECR sugerem um benefício no NEU geral medido pelo Teste de Bissecção de Linhas com estimulação cerebral não invasiva em comparação com placebo (SMD –2,35, IC 95% -3,72, -0,98; p = 0,0001; I2 = 85%); particularmente a EMTr produziu resultados que foram consistentes com a meta-análise geral (SMD -2,82, IC 95% -3,66, -1,98; p = 0,09; I2 = 0%). Os resultados de dois ECRs que comparam o EMTr com placebo também sugeriram um benefício no NEU geral medido pelo Motor Free Perception Test com EMTr 1Hz(SMD 1,46, IC 95% 0,73, 2,20; p <0,0001; I2 = 0%). Houve também um benefício no NEU global medido pelo Teste de Albert e Teste de Cancelamento de Linha com rTMS de 1 Hz em comparação com placebo (SMD 2,04, IC 95% 1,14, 2,95; p <0,0001; I2 = não aplicável). Os resultados também sugerem um possível melhora nas atividades da vida diária com EMTr de 10 Hz em comparação com

placebo (SMD 1,83, IC 95% 0,68, 2,97; p = 0,002; I2 = não aplicável).

Conclusões: Evidências de qualidade moderada mostram que o EMTr, com 1 Hz é mais eficaz que o placebo para negligência espacial unilateral após o AVC medido pelo Motor Free Perception Test. Além disso, evidências de baixa qualidade também sugerem um benefício da estimulação cerebral não-invasiva, particularmente com o uso de EMTr, para o NEU medido pelo Teste de Bissecção de Linha, Teste de Albert e Teste de Cancelamento de Linha. Esses achados devem ser explorados ainda mais no contexto da prática clínica entre neurologistas e fisioterapeutas.

ABSTRACT

Objective: A systematic review to investigate the impact of non-invasive brain stimulations (i.e., transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS), and theta-burst (TBS)) compared to sham for unilateral spatial neglect after stroke.

Data sources: Searches of MEDLINE, EMBASE, CENTRAL, CINAHL, and LILACS up to July 2017.

Study selection: Randomized controlled trials (RCTs) and non-RCTs.

Data extraction: Two pairs of reviewers independently screened potentially eligible articles, extracted data from included studies on populations, interventions and outcomes, and assessed their risk of bias. We used the GRADE approach to rate overall certainty of the evidence by outcome.

Data synthesis: 12 randomized trials including 273 participants, and four non-RCTs including 94 participants proved eligible. Results provided by RCTs suggest a benefit in overall USN measured by Line Bisection Test with non-invasive brain stimulations in comparison to sham (SMD -2.35, 95% CI -3.72, -0.98; p = 0.0001; I^2=85%); particularly the rTMS yielded results that were consistent with the overall meta-analysis (SMD -2.82, 95% CI -3.66, -1.98; p = 0.09; I^2=0%). Results from two RCTs comparing rTMS with sham also suggested a benefit in overall USN measured by Motor Free Visual Perception Test with 1 Hz (SMD 1.46, 95% CI 0.73, 2.20; p < 0.0001; I^2=0%). There was also a benefit in overall USN measured by Albert test and Line crossing test with 1 Hz rTMS compared to sham (SMD 2.04, 95% CI 1.14, 2.95; p <0.0001; I^2=not applicable). Results also suggest a possible increase in daily life functions with 10 Hz rTMS compared to sham (SMD 1.83, 95% CI 0.68, 2.97; p =0.002; I2=not applicable).

Conclusions: Moderate-quality evidence shows that rTMS, with 1 Hz, is more

efficacious compared to sham for unilateral spatial neglect after stroke measured by Motor Free Visual Perception Test. Furthermore, low-quality evidence also suggests a benefit of non-invasive brain stimulation, particularly with the use of rTMS, for overall USN measured by Line Bisection Test, Albert test and Line crossing test. These findings should be explored further in the context of the clinical practice among neurologists and physiotherapists.

1 BACKGROUND

Stroke is the second leading cause of death worldwide and the primary cause of chronic disability in adults [1]. In the United States, it is the fourth leading cause of death overall [2]. Among people who survive a stroke, unilateral spatial neglect (USN) is the most frequent disorder for right hemisphere lesions [3].

The incidence of USN varies widely from 10% to 82% [4-6]. USN is characterized by the inability to report or respond to people or objects presented on the side contralateral to the lesioned side of the brain and has been associated with poor functional outcomes and long stays in hospitals and rehabilitation centers.

Pharmacological interventions such as dopamine and noradrenergic agonists or pro-cholinergic treatment, have been used in people affected by USN after stroke, but the evidence derived from a Cochrane systematic review which included only two available RCTs was very low and inconclusive [7].

Other non-pharmacological rehabilitation techniques have been explored for USN with the aim to facilitate the recovery of perception and behavior which include right half-field eye-patching [8], mirror therapy [9], prism adaptation [10], left-hand somatosensory stimulation with visual scanning training [11], contralateral transcutaneous electrical nerve stimulation and optokinetic stimulation [12], trunk rotation [13], repetitive transcranial magnetic stimulation [14], galvanic vestibular stimulation [15], and dressing practice [16]. However, their results do not support use of these techniques in isolation for improvement of secondary outcomes such as performance and sensorimotor functions, activities of daily living (ADLs), or quality of life [9,14,17].

Non-invasive brain stimulations (transcranial Direct Current Stimulation (tDCS) and repetitive Transcranial Magnetic Stimulation (rTMS)) have already shown their

ability to modify cortical excitability [18]. The tDCS is a non-invasive method used to modulate cortical excitability by applying a direct current to the brain [19,20] which is less expensive than repetitive transcranial magnetic stimulation (rTMS). The latter is an electric current that creates magnetic fields penetrate the brain and can modulate cortical excitability by decreasing or increasing it and potentially improve cognitive abilities (including spatial neglect).

A previous Cochrane systematic review [21] summarized results about the effects of tDCS versus control (sham/any other intervention) in activities of daily living (ADLs) among stroke survivors. The authors included 32 randomized controlled trials (RCTs), and concluded that tDCS might enhance ADLs, but upper and lower limb function, muscle strength and cognitive abilities should be further explored [21]. Another Cochrane systematic review [22] assessed the efficacy of repetitive transcranial magnetic stimulation (rTMS) compared to sham therapy or no therapy for improving function in people with stroke. The 19 included trials showed that rTMS was not associated with a significant increase in ADLs neither on motor function, therefore the authors do not support the use of rTMS for the treatment of stroke, and they claimed for further trials to confirm their findings [22].

Previous reviews were, however, limited in that they did not include non-RCTs studies neither evaluated the newest non-invasive brain stimulation – thetaburst. We therefore conducted a systematic review of RCTs and non-RCTs studies that assessed the impact of tDCS, rTMS, and TBS for unilateral spatial neglect after stroke.

2 METHODS

We adhered to methods described in the Cochrane Handbook for Intervention Reviews [23]. Our reporting also adheres to the Preferred Reporting Items for Systematic Reviews and Meta-analyses [PRISMA] [24] and Meta-analysis of Observational Studies in Epidemiology [MOOSE] Statements [25].

2.1 Eligibility criteria

- Study designs: RCTs, quasi-RCTs, and non-RCTs.
- Participants: adults over 18 years of age, regardless of gender and the duration of illness or severity of the initial impairment, with USN after any type of stroke diagnosis (ischaemic or intracranial haemorrhage) measured by clinical examination or radiographically by computed tomography (CT) or magnetic resonance imaging (MRI), regardless of whether they were included after evaluation by a paper-and-pencil test.
- Interventions: any non-invasive brain stimulaitons such as tDCS; rTMS; including theta burst (continuous TBS (cTBS) or intermittent theta burst (iTBS). We considered to evaluate both the different type of stimulations (i.e., cathodal-tDCS versus anodal-tDCS versus dual-tDCS) and type of frequency (i.e., high-frequency versus low-frequency).
- Comparators: interventions were to be compared against sham stimulation; or any conventional stroke rehabilitation (e.g., pharmacological therapy; non-pharmacological therapy such as right half-field eye-patching, mirror therapy, prism adaptation, left-hand somatosensory stimulation, visual scanning training; or other conventional treatment).

We also considered non-invasive brain stimulations as an adjunct to any type of conventional stroke rehabilitation.

- Outcomes:
    - Overall USN measured by any paper-and-pencil tests, such as the Line Cancellation task [26], the Line Bisection test [27], or the Star Cancellation Test [28]; and by any validated specific instrument, such as the Catherine Bergego Scale [29] and the Behavioural Inattention Test [30].
    - Disability in neurological and functional abilities as measured by any validated specific instrument, such as the National Institutes of Health Stroke Scale and the Modified Rankin Scale [31], the Box and Block Test [32], or the Fugl-Meyer Assessment [33] after treatment and over the long term.
    - Daily life functions as measured by any validated measurement scale, such as the Barthel Index [31].
    - Number of reported falls as measured by diaries of falls, by the Morse Fall Scale [34], or by the Hendrich II Fall Risk Model [35] after treatment and over the long term.
    - Balance as measured by the Berg Balance Scale, the balance subscale of the Fugl-Meyer test, and the Postural Assessment Scale for Stroke Patients [36] after treatment and over the long term.
    - Depression or anxiety as measured by the Beck Depression Inventory, the Hospital Anxiety and Depression Scale, Symptom Checklist-90 (SCL-90), and the Hamilton Depression Rating Scale [37] after treatment and over the long term.

- Evaluation of poststroke fatigue by the Fatigue Severity Scale [38] after treatment and over the long term.
- Quality of life (however defined by the study authors) after treatment and over the long term.
- Adverse events (eg, euphoria, hallucinations, orthostatic hypotension, nausea, insomnia, dizziness, syncope) after treatment and over the long term.
- Death.

2.2 Data source and searches

We searched MEDLINE (OvidSP) (1966 to July 2017), EMBASE (OvidSP) (1980 to July 2017), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, 2017, issue 7), CINAHL (1961 to July 2017), and Latin-American and Caribbean Center on Health Sciences Information (LILACS) (from 1982 to July 2017) without language restrictions. The date of the most recent search was 26 July 2017 (Appendix table 1). All searches were conducted with the assistance of a trained medical librarian. We also searched the reference lists of relevant articles and conference proceedings and contacted the authors of included trials.

Appendix table 1. Search strategy*.

(tDCS OR TDCS OR Cathodal Stimulation Transcranial Direct Current Stimulation OR Cathodal Stimulation tDCSs OR Cathodal Stimulation tDCS OR Transcranial Random Noise Stimulation OR Transcranial Alternating Current Stimulation OR Transcranial Electrical Stimulation OR dual transcranial direct current stimulation OR Transcranial Electrical Stimulations OR Anodal Stimulation Transcranial Direct Current Stimulation OR Anodal Stimulation Tdcs OR Anodal Tdcs OR Anodal Stimulation TDCSs OR Repetitive Transcranial Electrical Stimulation OR repetitive transcranial magnetic stimulation OR RTMS OR rTMS OR High-frequency rTMS OR Trasncranial Magnetic Stimulation OR Transcranial Magnetic Stimulations OR Low-frequency transcranial magnetic stimulation OR Stimulation Transcranial Magnetic OR Stimulations

Transcranial Magnetic OR Single Pulse Transcranial Magnetic Stimulation OR Paired Pulse Transcranial Magnetic Stimulation OR Repetitive Transcranial Magnetic Stimulation OR theta burst OR theta burst stimulation OR theta-burst OR theta-burst stimulation OR burst stimulation OR continuous theta burst stimulation OR continuous TBS OR TBS) AND (cerebrovascular disorders OR basal ganglia cerebrovascular disease OR hemispatial neglect OR hemispatial neglect OR spatial attentional asymmetries OR brain ischemia OR carotid artery diseases OR intracranial arterial diseases OR intracranial embolism and thrombosis OR intracranial hemorrhages OR stroke OR brain infarction OR vertebral artery dissection OR post-stroke OR poststroke OR hemineglect OR hemi-neglect OR unilateral visuospatial neglect OR visuospatial neglect OR visual spatial neglect OR spatial neglect OR unilateral neglect of acute stroke patients OR unilateral spatial neglect OR patients with stroke OR stroke patients with spatial neglect OR right hemisphere strokes OR rehabilitation after stroke OR chronic spatial neglect after stroke OR unilateral neglect OR spatial neglect OR hemispatial neglect OR visual neglect OR inattention OR hemi-inattention OR space perception OR visual perception OR perceptual disorders OR perceptual disorder OR extinction OR functional laterality)

*Limited for humans, clinical trials, and observational studies.

2.3 Selection of studies

Two pairs of reviewers independently screened all titles and abstracts identified by the literature search, obtained full-text articles of all potentially eligible studies, and evaluated them for eligibility. Reviewers resolved disagreement by discussion or, if necessary, with third party adjudication. We also considered studies reported only as conference abstracts.

2.4 Data extraction

Reviewers underwent calibration exercises, and worked in pairs to independently extract data from included studies. They resolved disagreement by discussion or, if necessary, with third party adjudication. They abstracted the following data using a pre-tested data extraction form: study design; participants; interventions; comparators; outcome assessed; and relevant statistical data.

2.5 Risk of bias assessment

Reviewers, working in pairs, independently assessed the risk of bias of included RCTs using a modified version of the Cochrane Collaboration's instrument [39] [http:/distillercer.com/resources/] [40]. That version includes nine domains: adequacy of sequence generation, allocation sequence concealment, blinding of participants and caregivers, blinding of data collectors, blinding for outcome assessment, blinding of data analysts, incomplete outcome data, selective outcome reporting, and the presence of other potential sources of bias not accounted for in the previously cited domains [40]. For incomplete outcome data in individual studies we stipulated as low risk of bias for loss to follow-up of less than 10% and a difference of less than 5% in missing data between intervention/exposure and control groups.

When information regarding risk of bias or other aspects of methods or results was unavailable, we attempted to contact study authors for additional information.

2.6 Certainty of evidence

We summarized the evidence and assessed its certainty separately for bodies of evidence from RCTs and non-RCTs studies. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate certainty of the evidence for each outcome as high, moderate, low, or very low [41]. In the GRADE approach RCTs begin as high certainty and non-RCTs studies as moderate certainty. Detailed GRADE guidance was used to assess overall risk of bias [42], imprecision [43], inconsistency [44], indirectness [45] and publication bias [46], and to summarize results in an evidence profile.

We planned to assess publication bias through visual inspection of funnel plots for each outcome in which we identified 10 or more eligible studies; however we were

not able because there were an insufficient number of studies to allow for this assessment.

2.7 Data synthesis and statistical analysis

We calculated pooled inverse variance standardized mean difference (SMD) and associated 95% CIs using random-effects models. We addressed variability in results across studies by using I^2 statistic and the P value obtained from the Cochran chi square test. Our primary analyses were based on eligible patients who had reported outcomes for each study (complete case analysis). We used Review Manager (RevMan) (version 5.3; Nordic Cochrane Centre, Cochrane) for all analyses [47].

2.8 Subgroup and sensitivity analyses

We planned possible subgroup analyses according to the characteristics of:

- Participants (stroke type: ischaemic stroke versus intracranial haemorrhage).
- Interventions (type of stimulation: cathodal versus anodal and position of electrodes; type of frequency (high-frequency versus low-frequency).
- Comparator (type of control intervention: pharmacological therapy versus non-pharmacological).
- Different tests for overall USN (Star Cancellation test versus Line Bisection Test).

We planned to conduct subgroup analyses only when five or more studies were available, with at least two in each sub-group. We planned to synthesize the evidence separately for bodies of evidence from RCTs and non-RCTs studies by a sensitivity analysis.

3 RESULTS

3.1 Study selection

We identified a total of 4,129 citations through database searches and further four studies from the reference lists of the Cochrane reviews [22,48,49] (see Figure 1 for search results). After screening by title and then by abstract, we obtained full-paper copies for 30 citations that were potentially eligible for inclusion in the review. We excluded 15 studies for the following reasons: case report, case series, self-controlled study, review and, off-topic. The remaining 11 RCTs [14, 50-59] with a total of 256 participants, and four non-RCTs [60-63] with a total of 94 participants, met the minimum requirements, and we included them in this review.

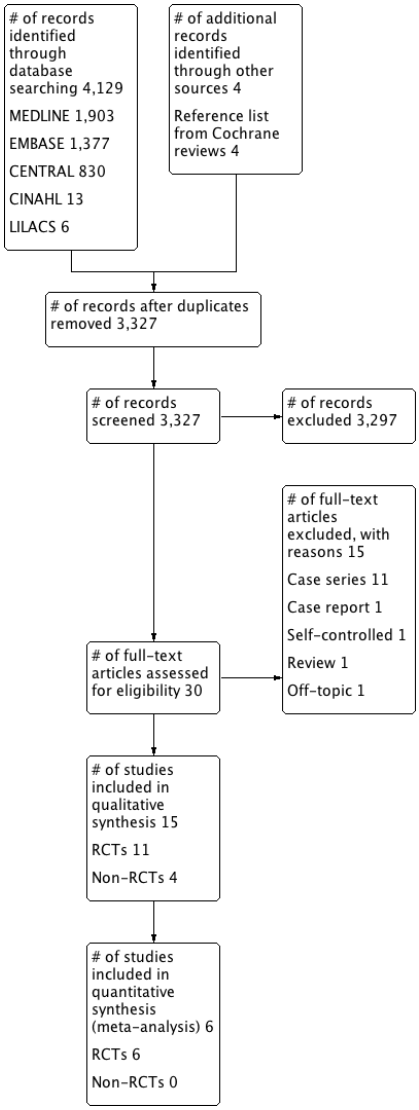


Figure 1 - Flow diagram of the systematic review

3.2 Study characteristics

Table 1 describes study characteristics related to design of study, setting, number of participants, mean age, gender, inclusion and exclusion criteria, and follow-up. Eight studies [14, 54, 56, 59, 60-63] were conducted largely in Europe, and eight in Asia [50-53, 55, 57, 58, 65]. Randomized trials sample size ranged from 10 [56] to 38 [55], and non-RCTs studies from 12 [62] to 36 [61]. Typical participants were males in their 40s, 50s and 60s. Studies followed participants immediately after treatment [50, 57, 58, and 61] to one month [51, 52, 54-56].

Table 1 - Study characteristics related to design of study, setting, number of participants, mean age, gender, and inclusion and exclusion criteria.

Author, year	Design of study	Status of publication	Location	No.* participants	Mean age	No. male (%)	Inclusion criteria	Exclusion criteria
Randomized controlled trials								
Cao 2016 [50]	Parallel RCT	Full-text	Asia	I: 7 C: 6	I: 55.0 C: 62.0	I: 85.7 C: 83.3	Right-handed patients who had a first-ever stroke in the right hemisphere and visuospatial neglect with normal or corrected to normal vision.	NR
Cha 2016 [51]	Parallel RCT	Full-text	Asia	I: 15 C: 15	I: 64.07 C: 63.33	I: 64 C: 60.0	had a first right hemisphere stroke (cerebral infarction or hemorrhage) more than 2 weeks before the study, which had been confirmed by computed tomography or magnetic resonance imaging (MRI); had VSN determined by line bisection tests (rightward bias >12%) or star cancelation test (omission of any number of stars); had a Glasgow coma scale score <15; 18–80 years old; right-handed; normal vision or normal corrected vision; and had the ability to understand the study and sign an informed consent form.	All patients did not have brain tumors or other brain pathology. Excluded were patients with hemianopia; subarachnoid hemorrhage, venous sinus thrombosis, transient ischemic attack, reversible ischemia, or a condition exacerbated by a new infarction or hemorrhage site; a medical history or family history of seizure; or with metal devices or claustrophobia preventing MRI.

Fu 2015 [52]	Parallel RCT	Full-text	Asia	I: 11 C: 11	I: 55.1[β] C: 59.5[β]	I: 80.0 C: 80.0	Right handed patients with right hemisphere stroke (haemorrhagic or ischaemic lesion) confirmed by computed tomography or magnetic resonance imaging >2 weeks before the beginning of the study and diagnosis of visuospatial neglect based on clinician judgement and on deficits in at least one out of two paper–pencil tests.	Age <30 years or >80 years, history of epilepsy, previous head trauma, drug and alcohol abuse and psychiatric disorders, recurrent stroke, obvious aphasia and communication obstacles, family history of seizures, ever use of tricyclic antidepressants or antipsychotic drugs, diamagnetic metal implants such as cardiac pacemakers, and visual field defects.
Fu 2017 [65]	Parallel RCT	Full-text	Asia	I: 6 C: 6	I: 60.17 C: 62	I: 75 C: 75	had a first right hemisphere stroke (cerebral infarction or hemorrhage) more than 2 weeks before the study, which had been confirmed by computed tomography or magnetic resonance imaging (MRI); had VSN determined by line bisection tests (rightward bias >12%) or star cancelation test (omission of any number of stars); had a Glasgow coma scale score <15; 18–80 years old; right-handed; normal vision or normal corrected vision; and had the ability to understand the study and sign an informed consent form. All patients did not have brain tumors or other brain pathology.	patients with hemianopia; subarachnoid hemorrhage, venous sinus thrombosis, transient ischemic attack, reversible ischemia, or a condition exacerbated by a new infarction or hemorrhage site; a medical history or family history of seizure; or with metal devices or claustrophobia preventing MRI. history or family history of seizure; or with metal devices or claustrophobia preventing MRI.
Smit 2015 [56]	RCT cross-over study	Full-text	Europe	I: 5[€] C: 5[€]	I: 64.8[€] C: 64.8[€]	I: 60.0[€] C: 60.0[€]	Patients with left hemi-spatial neglect after right hemispheric lesion, right-handed, older than the age of 18, more than four months after stroke.	Patients with severe language and communication disorders, bilateral cortical damage, psychiatric disorders, alcohol and/or drug addiction, epilepsy, eczema or damages on the scalp, metal or other foreign parts in the head.

Yang 2015 [55]	Parallel RCT	Full-text	Asia	I: 9 I2: 10 I3: 9 C: 10	I: 46.7 I2: 48.0 I3: 49.4 C: 47.7	I: 66.6 I2: 40.0 I3: 55.6 C: 30.0	Age between 18-80; first stroke patients (cerebral infarction or hemorrhage) and in recovery time within 60-180 days; USN confirmed by line bisection test, star cancellation test or clinical examination; no metallic implant of diamagnetic substance; signed the informed consent.	Subarachnoid hemorrhage, venous sinus thrombosis, reversible or transient ischemic attacks; worsening condition, new-onset infarction or hemorrhage ; GCS score <15; obvious aphasia, severe cognitive-communication disorders; family history of epilepsy; impaired organ function or failure in heart, lung, liver, kidney or other vital organs, and life expectancy < 6months; history of claustrophobia and uncooperative during examination; hemianopsia.
Kim 2013 [53]	Parallel RCT	Full-text	Asia	I: 9 I2: 9 C: 9	I: 68.6 I2: 64.1 C: 68.3	I: 55.6 I2: 44.4 C: 66.7	Patients with right cerebral ischemic or hemorrhagic with visuospatial neglect (confirmed using the line bisection test). All patients were right-handed.	Severe cognitive impairment making them unable to understand the instructions; contraindications for TMS, such as a history of epileptic seizure, major head trauma, presence of metal in the skull or pacemaker; or unstable medical or neurologic conditions.
Sunwoo 2013 [57]	RCT cross-over study	Full-text	Asia	I: 10 I2: 10 C: 10	62.6[¢]	40.0[β]	Stroke patients with lesion in the right hemisphere involving the parietal cortex, and left USN diagnosed by clinical observation and confirmed by a line bisection test. All patients were previously right-handed.	Patients who had metallic implants in the cranial cavity, a skull defect, history of seizure, uncontrolled medical problems, and severe cognitive impairment.
Cazzoli 2012 [14]	Parallel RCT	Full-text	Europe	24[£]	58.0[¢]	70.8[¢]	Ischaemic or haemorrhagic lesion to the right hemisphere and left-sided spatial neglect determined on the basis of deficits in at least two out of three classes of paper-pencil tests and on clinical judgement. All patients had to have normal or corrected-to-normal visual acuity.	History of epilepsy, prior head trauma, drug and alcohol abuse and major psychiatric disorders.

Ko 2008 [58]	RCT cross-over study	Full-text	Asia	I: 15[€] C: 15[€]	I: 62.1[€] C: 62.1[€]	I: 66.6[€] C: 66.6[€]	Patients with sub acute stroke with neglect.	Patients who had metal in the cranial cavity or calvarium, skin lesions in the area of electrode, uncontrolled medical conditions, severe cognitive impairments.
Koch 2012 [54]	Parallel RCT	Full-text	Europe	I: 10 C: 10	I: 61.4[#] C: 71.9[#]	I: 55.5[#] C: 55.5[#]	Right-handed patients, with right hemisphere sub acute ischemic stroke affected by hemispatial neglect, confirmed by radiologic (CT or MRI) and clinical examination.	NR
Bonni 2011 [59]	Parallel RCT	Conference abstract	Europe	NR	NR	NR	Sub acute stroke patients with neglect.	NR
				Non-RCTs				
Cazzoli 2015 [60]	Non-RCT cross-over study[§]	Full-text	Europe	I: 8[¥] C: 8[¥]	I: 52.6 and 54.2[α] C: 53.0	NR	Patients with left-sided, hemispatial neglect after a sub acute right-hemispheric stroke. All patients had normal or corrected-to-normal visual acuity.	Not clearly reported, however, authors have assessed patients by means of internationally accepted safety guidelines for the application of TMS, which included screening for a history of epilepsy, prior head trauma, drug and alcohol abuse and major psychiatric disorders.
Hopfner 2015 [61]	Non-RCT cross-over	Full-text	Europe	I: 18[€] C: 18[€]	I: 64.5[€] C: 64.5[€]	I: 50.0[€] C: 50.0[€]	Left-sided neglect, based on clinical judgement and neuropsychological testing, after sub acute right-hemispheric stroke. All subjects had normal or corrected-to-normal visual acuity.	NR
Làdavas 2015 [63]	Quasi-RCT	Full-text	Europe	I: 8 I2: 11 C: 11	I: 72.0 I2: 66.0 C: 67.0	I: 50.0 I2: 54.5 C: 54.5	Patients with right hemisphere stroke with hemispatial neglect and performance on the Behavioral Inattention Test battery with scores ≤129.	Presence of widespread mental deterioration (Mini-Mental State Examination score <20), psychiatric disorders, a history of prior stroke or haemorrhage, any severe internal medical disease, epilepsy and additional factors influencing the risk of epilepsy.

Agosta 2014 [62]	Non-RCT cross-over study	Full-text	Europe	I: 6[€] C: 6[€]	I: 67.83[€] C: 67.83[€]	I: 66.6[€] C: 66.6[€]	Patients with right hemisphere unilateral lesions due to a cerebrovascular stroke, confirmed by radiological examination (CT or MR), in their chronic stage after the stroke (at least six months post-onset). Besides, participants were right-handed, native Italian speakers, and had normal or corrected-to-normal visual acuity.	History or evidence of degenerative disease or psychiatric disorder.

C: control group; CT: computed tomography; GCS: Glasgow Coma Scale; I: intervention; MR: Magnetic resonance imaging; no.: number; RCT: randomized controlled trial; TMS: transcranial magnetic stimulation; USN: Unilateral spatial neglect;
[€]Participants of the experimental group also served as controls.
[¥]Five patients were randomized in parallel design, and three further patients included in both groups.
[£]The authors did not specify the sample size per studied group.
[α]Data comprises three patients that received both experimental and control interventions.
[β]Data was calculated from 10 patients (one patient was excluded after randomization).
[¢]Data are from the whole sample, as the authors did not specify it per studied group.
[#]Data are from 9 patients in each group.
[§]The study was a cross-over for only three patients, for the remaining ten patients the study was a RCT.

Table 2 describes study characteristics related to intervention and comparators, and assessed outcomes. Of the 15 included studies, eight trials [14, 50, 52, 54, 55, 59, 60, and 61] evaluated TBS:

- Eight trials compared cTBS versus:
    - sham cTBS, both groups received conventional rehabilitation training [52,65];
    - 1 Hz rTMS, 10 Hz rTMS, and sham rTMS, all groups with addition of routine rehabilitation [55];
    - sham TBS [14];
    - sham cTBS [54,59,60,61].
- One trial compared iTBS with 80% resting motor threshold (RMT) versus iTBS 40% RMT [50].

Of the remaining seven studies, four trials [56-58,63] evaluated tDCS:

- Two trials compared tDCS over the left (cathodal) and right (anodal) posterior parietal cortex, one versus placebo at an intensity of 2mA [56], and the other versus sham tDCS [63];
- One trial [57] compared tDCS dual versus either tDCS single or tDCS sham;
- One trial [58] compared tDCS versus sham tDCS.

Three further trials [51,53,62] evaluated rTMS:

- One trial [51] compared rTMS with sham rTMS, both plus conventional rehabilitation therapy (neurodevelopmental facilitation techniques);
- Two trials compared 1 Hz rTMS, one versus and 10 Hz rTMS and sham rTMS [53] (both groups received conventional rehabilitation); and the other trial compared 1 Hz rTMS versus sham rTMS [62].

None of the included study evaluated non-invasive brain stimulations as an adjunct to any type of conventional stroke rehabilitation.

Table 2 - Study characteristics related to intervention and control groups, assessed outcomes, and follow-up.

Author, year	Description of interventions	Description of control groups	Measured outcomes	Follow-up
Randomized controlled trials				
Cao 2016 [50]	**iTBS** 80% RMT in the rTMS group. Stimulation was applied using an 87-mm butterfly coil connected to a Magstim rapid2 (Magstim Co., Whitland, UK), with peak intensity of 2.0 T and a maximum pulse length of 250 μs. Pulses (theta burst type) were delivered to the left dorsal lateral prefrontal cortex, the F5 label of the left hemisphere, which is between the F3 and F7, at 80% of resting motor threshold. Two sessions were applied with a 15-min interval on each day. Each session included 20 stimulation trains consisting of three pulses delivered at a frequency of 50 Hz in every 200 ms for 2 s (total 10 bursts, 30 pulses) with an interval of 8 s.	Same as intervention group, however, pulses were delivered at 40% of RMT.	Line Bisection and Star Cancellation tests.	After intervention.
Cha 2016 [51]	**Repetitive rTMS** + conventional rehabilitation therapy (neurodevelopmental facilitation techniques) for a total of 40 minutes (rTMS: 10 min; rehabilitation: 30 min) per day, with a 10-minute rest period halfway through the session, for 4 weeks, 5 days per week. Stimulation was delivered using figure-of-eight coil with a diameter of 80mm connected to Magstim Rapid2 (Magstim co., Ltd, Wales, UK). Stimulation was applied in right posterior parietal (P3 and P4 areas) based on the electroencephalogram 10/20 system at a frequency of 1 Hz for 5 minutes with 90% of the motor threshold during rest.	Sham rTMS and conventional rehabilitation therapy using the same protocol than the experimental group.	Motor Free Visual Perception Test; Line Bisection Test; Albert Test; Star Cancellation Test.	4 weeks
Fu 2015 [52]	Left posterior parietal cortex **cTBS** + conventional rehabilitation training. cTBS was set over P5, three-pulse burst was delivered at 30 Hz and repeated every 200 ms for 40 s with intensity was 80% of the resting motor threshold. cTBS was delivered using a Super Rapid 2 magnetic stimulator (Magstim, Whitland, UK) with 2.0-Tesla maximum field strength, connected with a figure-of-eight coil (diameter of outside loop, 87 mm). Patients received 4 trains	Sham cTBS + conventional rehabilitation training.	Star Cancellation Test; Line Bisection Test.	4 weeks

	daily, with an interval of 15 min, for 14 consecutive days.			
Fu 2017 [65]	The cTBS group received continuous TBS with the coil placed tangentially to the scalp at P3 over the left posterior parietal cortex (according to the 10–20 electrode position system of the American Electroencephalographic Association28). The magnitude of the pulses was maintained at 80% resting motor threshold. On each day for 10 consecutive days, 4 sessions of stimulation were delivered, with an interval of 15 min between every 2 sessions. Each session lasted 40 s and contained 600 pulses delivered in 200 bursts at 5 Hz (theta rhythm). Each burst included 3 pulses delivered at 30 Hz.	The active control group received stimulations with the same features at the same position as the cTBS group, but with the coil placed perpendicular to the scalp surface and the amplitude of the stimulation pulses reduced to 40% resting motor threshold	Star Cancellation Test; Line Bisection Test.	10 days
Smit 2015 [56]	**tDCS** was applied for 20 minutes over the left (cathodal) and right (anodal) posterior parietal cortex on five consecutive days with a battery-driven direct current stimulator (NeuroConnDC-Stimulator; serialnumber 0096). Stimulation parameters were set at a current of 2000 mA, and a resistance of <10kOhm, applied for 1200s with ramping up in 30s and ramping down in 30s. Electrodes were located over the posterior parietal lobe, corresponding with P3 (cathodal electrode) and P4 (anodal electrode). Treatment conditions were separated by a four weeks wash-out period.	Placebo was applied for 20 minutes over the left (cathodal) and right (anodal) posterior parietal cortex at an intensity of 2mA on five consecutive days. Treatment conditions were separated by a four weeks wash-out period.	Cancellation Tests; Line Bisection Tests; Drawing Tests.	1 month
Yang 2015 [55]	Group I: 1 Hz **rTMS** two times a day for 2 weeks + routine rehabilitation. Stimulation was administered using a rapid magnetic stimulator (Magstim Company) with a figure-of-eight coil, peak intensity of stimulation at 2 T and pulse duration of 250 s, at the contralateral hemisphere (P3), intensity 80% of RMT, frequency 1 Hz and stimulus duration for each sequence was 8 s, repeated 82 sequences with a total of 656 pulse number. Group I2: 10 Hz **rTMS** two times a day for 2 weeks + routine rehabilitation. Stimulation was administered using a rapid magnetic stimulator (Magstim Company) with a figure-of-eight coil, peak intensity of stimulation at 2 T and pulse duration of 250 s, at the contralateral hemisphere (P3), intensity 80% of RMT, frequency	Sham rTMS two times a day for 2 weeks + routine rehabilitation.	Star Cancellation Test; Line Bisection Test.	1 month

	10 Hz, with a total pulse number of 1000 and stimulation interval of 55 s. Group I3: **cTBS** two times a day for 2 weeks + routine rehabilitation. Stimulation was administered using a rapid magnetic stimulator (Magstim Company) with a figure-of-eight coil, peak intensity of stimulation at 2 T and pulse duration of 250 s, at the contralateral hemisphere (P3), intensity 80% of RMT. 801 pulses, in bursts of 3 pulses at 30 Hz, repeated every 100ms.			
Kim 2013 [53]	Group A: 10 sessions of low-frequency (**1Hz**) **rTMS** over the nonlesioned left posterior parietal cortex (P3) at a 90% motor threshold in 4 trains of 5-minute duration, each separated by 1 minute (resulting in a total stimulation period of 20 minutes). rTMS was delivered using a Magstim Super Rapid Magnetic Stimulatora with a 70-millimeter, air-cooled 8 shaped coil. rTMS was performed 5 times per week for 2 weeks. Patients also received conventional rehabilitation treatment (including physical, occupational, and cognitive therapies). Group B: 10 sessions of high-frequency (**10Hz**) **rTMS** over the lesioned right posterior parietal cortex (P4) at a 90% motor threshold in 4 trains of 5-minute duration, each separated by 55 seconds (resulting in a total stimulation period of 20 minutes). The remaining of the protocol followed the same instructions as group A.	Sham rTMS + conventional rehabilitation.	Motor-Free Visual Perception Test; Line Bisection Test; Cancellation Test; Catherine Bergego Scale; Korean-Modified Barthel Index.	2 weeks
Sunwoo 2013 [57]	Group A: Dual-mode (**tDCS dual**) direct current was delivered by two sets of battery-powered devices (Phoresor II Auto Mod-elPM850, IOMED, USA) using two pairs of surface saline-soaked sponge electrodes (5 cm × 5 cm). Anodal tDCS of the first circuit over the right PPC (P4) was accompanied by cathodal tDCS of the second circuit over the left PPC (P3). Therefore, in the first tDCS circuit, the anode was placed over P4 and the cathode was placed over the left supraorbital area. In the second tDCS circuit,the anode	Sham mode (tDCS sham) in the first and second tDCS circuits. The stimulator was turned on and the current intensity was gradually increased for 5s, and was then tapered off over 5s.	Line Bisection Test; Star Cancelation Test.	Immediately after treatment.

	was placed over the right supraorbital area and the cathode was placed over the P3. A constant current of 1 mA was delivered for 20 min. Group B: Single-mode (**tDCS single**) direct current was delivered by two sets of battery-powered devices (Phoresor II Auto Model PM850, IOMED, USA) using two pairs of surface saline-soaked sponge electrodes (5 cm × 5 cm). The anode was placed over P4 and the cathode over the left supraorbital area (the first tDCS circuit) and real stimulation was provided, whereas the second tDCS circuit received sham stimulation. For the real stimulation, a constant current of 1 mA was delivered for 20 min. For the sham stimulation, the stimulator was turned on and the current intensity was gradually increased for 5s, and was then tapered off over 5s.			
Cazzoli 2012 [14]	**cTBS** for 2 days on week 1 and sham TBS for 2 days on week 2. cTBS was applied by means of a MagPro X100 stimulator (Medtronic Functional Diagnostics) connected to a round coil with 60mm outer radius (Magnetic Coil Transducer MC-125). cTBS protocol comprised 801 pulses, delivered in a continuous train and consisting of 267 bursts, each one contained three pulses at 30Hz, repeated at 6Hz (total duration of one single, cTBS train was 44s) and eight cTBS trains were applied over 2 days. cTBS was applied over P3. Besides, patients received neurorehabilitation therapy including 1h neuropsychological training, 1h of occupational therapy and 1h of physiotherapy per day.	Control A: sham TBS for 2 days on week 1 and cTBS for 2 days on week 2. cTBS protocol was the same described for intervention A. Besides, patients received neurorehabilitation therapy including 1h neuropsychological training, 1h of occupational therapy and 1h of physiotherapy per day. Control B: sham TBS for 2 days on week 1 and sham TBS for 2 days on week 2. Besides, patients received neurorehabilitation therapy including 1h neuropsychological training, 1h of occupational therapy and 1h of physiotherapy per day.	Catherine Bergego Scale; Vienna Test System; random shape cancelation test.	2 weeks

Ko 2008 [58]	**tDCS** to the right posterior parietal cortex for 20 min (2mA anodal DC brain polarization) delivery by a battery-powered device (Phoresor II Auto model PM850, IOMED, USA), using a pair of saline-soaked surface sponge electrodes (5cm x 5cm). The anode was placed over P4 and cathode was placed over left supraorbital area.	Sham tDCS (current was delivered for 10s and then turned off).	Line Bisection Test; shape-unstructured cancellation test; letter-structured cancellation test.	Immediately post intervention.
Koch 2012 [54]	**cTBS** was delivered using a MagStim Super Rapid magnetic stimulator (Magstim Company, Whitland, Wales, UK), connected with a figure-ofeight coil with a diameter of 70 mm. In each session, 3-pulse bursts at 50Hz repeated every 200 msec for 40 s were delivered at 80% of the active motor threshold over the left PPC (600 pulses). Every day 2 sessions of left PPC cTBS were applied with an interval of 15 minutes and lasted for 10 days (5 days per week, Monday to Friday). Patients also received rehabilitation program consisted of 20 sessions of 45 minutes each, held 5 days per week (based on computerized visuospatial scanning training) and motor rehabilitation when necessary.	Sham cTBS was delivered with the coil angled at 90°, with only the edge of the coil resting on the scalp. Stimulus intensity, expressed as a percentage of the maximum stimulator output, was set at 80% of the active motor threshold inducing the same acoustic sensation as for real TBS. Patients also received rehabilitation program.	Line crossing test; Letter Cancellation test; Star Cancellation test; Figure and Shape Copying Test; Representative Drawing Test;	1 month
Bonni 2011 [59]	**cTBS** over the left PPC, for two weeks.	Sham cTBS.	Standardized behavioural inattention test; excitability of the parieto-frontal functional connections.	NR
		Non-RCTs		
Cazzoli 2015 [60]	**cTBS** over the left, contralesional PPC (P3), was applied using a MagPro X100 stimulator, connected to either a round coil (MC-125 Medtronic Functional Diagnostics). The cTBS protocol consisted of 801 pulses delivered in a continuous train. The train was comprised of 267 bursts, which each contained three single pulses at 30 Hz, repeated at 6 Hz, and had a total duration of 44s. Application consisted on two trains separated by a 15 min interval.	Sham cTBS over the left, contralesional PPC, was applied using a sham coil (MC-P-B70 Medtronic Functional Diagnostics).	Computerised Balloons test with eye movement recording; Paper-pencil cancellation tasks.	8 hours

Hopfner 2015 [61]	**cTBS** comprised 801 pulses, delivered in a continuous train of 267 bursts (each including 3 pulses at 30Hz, repeated at 6Hz). The total duration of a single cTBS train was 44s. Two cTBS trains were applied overP3, with an inter-train interval of 15min. A MagPro X100 stimulator (Medtronic Functional Diagnostics, Farum, Denmark), connected to around coil (Magnetic Coil Transducer MC-125) was used to deliver biphasic, repetitive magnetic pulses. Besides 12 (from 18) patients also received Smooth pursuit eye movement training.	Sham cTBS connected to a placebo coil (Magnetic Coil Transducer MC-P-B70). Besides 12 (from 18) patients also received Smooth pursuit eye movement training.	Center of Cancellation score; x-position of leftmost cancelled target; Number of cancelled targets.	Right after treatment.
Làdavas 2015 [63]	Group A: 2-week rehabilitation program consisted of 10 sessions of **cathodal tDCS** lasting 30 minutes each and held 5 days per week. tDCS was applied using a battery-driven Eldith (neuroConn GmbH, Ilmenau, Germany) Programmable Direct Current Stimulator with a pair of surface saline-soaked sponge electrodes. In each session was delivered a constant current of 2mA intensity (current density: 0.57 mA/cm2) lasting 20 minutes of cathodal tDCS of the left, intact PPC (over P5). Group B: 2-week rehabilitation program consisted of 10 sessions of **anodal tDCS** lasting 30 minutes each and held 5 days per week. The anodal tDCS was placed over the PPC of the damaged hemisphere (P6). The remaining protocol was the same used in the Group A.	Sham tDCS (montage used in the sham group mimicked that used in the two active groups).	Behavioral Inattention Test.	Final follow-up within the first week after the last session.
Agosta 2014 [62]	A 10-minute train of repetitive low frequency (**1Hz**) **rTMS** over the left parietal lobe (P3 site) identified using the 10/20 EEG measurement system. The stimulus was delivered using a 70mm figure-8-coil connected to a Magstim Rapid2 (Magstim Co., UK). Stimulation strength was set to 90% of the threshold to evoke motor responses at rest.	Sham rTMS over the intact left parietal cortex.	Visual tracking task; unilateral and bilateral tasks.	30 minutes

C: control group; cTBS: continuous theta burst stimulation; I: intervention; iTBS: intermittent theta burst; PPC: posterior parietal cortex; RMT: resting motor threshold; rTMS: repetitive transcranial magnetic stimulation; tDCS: transcranial direct current stimulation; TBS: theta Burst Stimulation; USN: Unilateral spatial neglect.

3.3 Risk of bias

Figures 2 and 3 describe the risk of bias assessment for the RCTs and non-RCTs, respectively. The major issue regarding risk of bias in the RCTs and non-RCTs was problems of random sequence generation [14,50,51,54-59,60-63] and concealment of randomization [14,50,53-59,60-63]. Additional problems was blinding of statistician in all included studies.

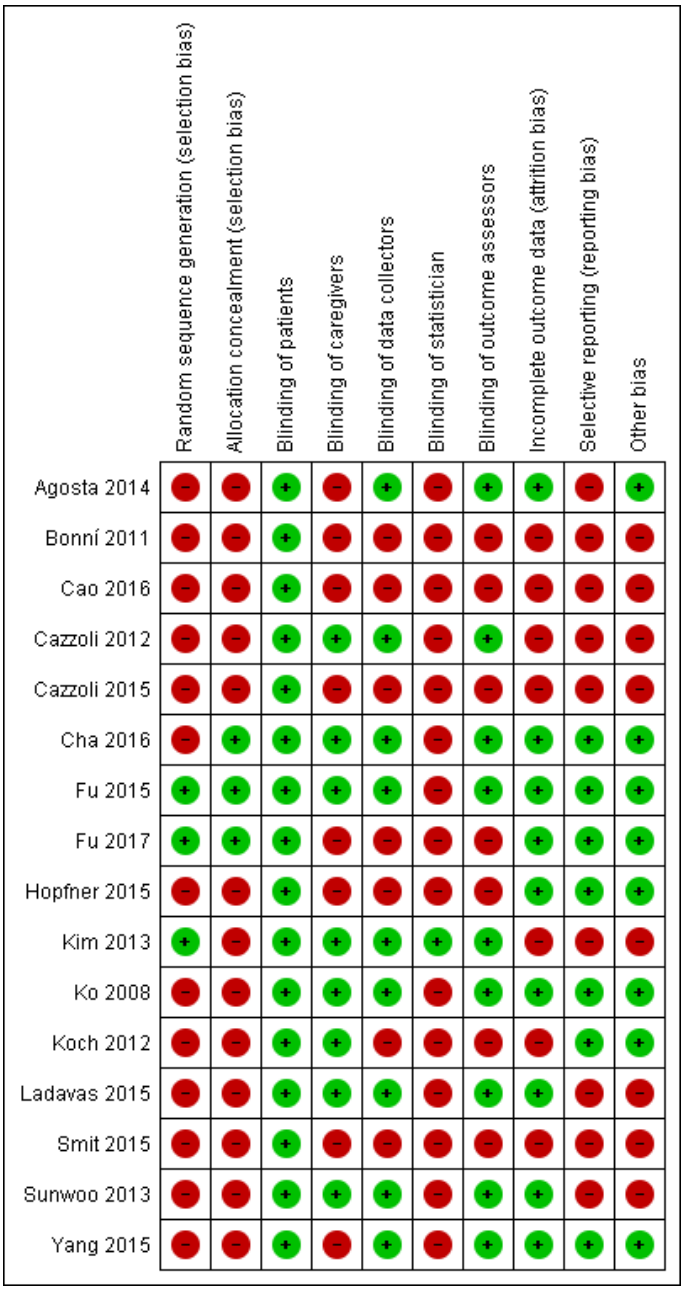


Figure 2 - Risk of bias assessment for RCTs.

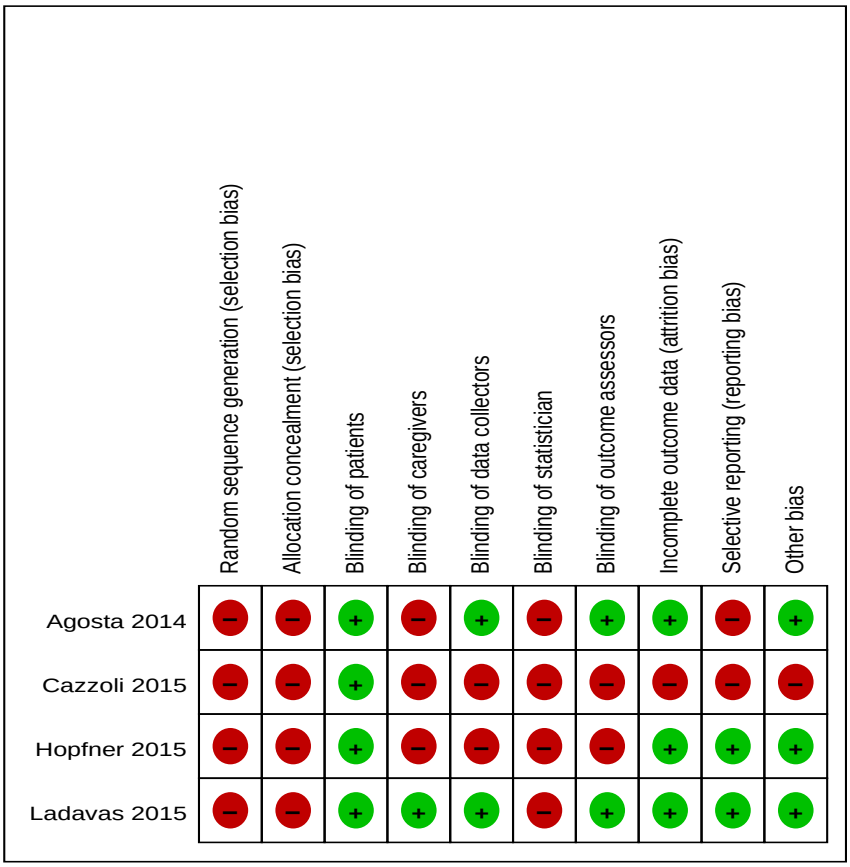


Figure 3 - Risk of bias assessment for non-RCTs.

Table 3 - Risk of bias assessment for the RCTs and non-RCTs.

Author, year	Was the randomization sequence adequately generated?	Was allocation adequately concealed?	Was there blinding of patients?	Was there blinding of caregivers?	Was there blinding of data collectors?	Was there blinding of statistician?	Was there blinding of outcome assessors?	Was loss to follow-up (missing outcome data) infrequent?*	Are reports of the study free of suggestion of selective outcome reporting?	Was the study apparently free of other problems that could put it at a risk of bias?
Randomized controlled trials										
Bonni 2011 [59]	Probably no	Probably no	Probably yes	Probably no	Probably no	Probably no	Probably no	Probably no	Probably no	Probably no
Cao 2016 [50]	Probably no	Probably no	Probably yes	Probably no	Probably no	Probably no	Probably no	Probably yes	Probably no	Probably yes
Cazzoli 2012 [14]	Probably no	Probably no	Definitely yes	Probably yes	Definitely yes	Probably no	Definitely yes	Probably yes	Probably yes	Probably yes
Cha 2016 [51]	Definitely no	Definitely yes	Definitely yes	Definitely yes	Definitely yes	Probably no	Definitely yes	Probably yes	Probably yes	Probably yes
Fu 2015 [52]	Definitely yes	Probably yes	Definitely yes	Definitely yes	Probably yes	Probably no	Probably yes	Probably yes	Probably yes	Probably yes
Fu 2017 [65]	Probably yes	Probably yes	Probably yes	Probably no	Probably no	Probably no	Probably no	Definitely yes	Probably yes	Definitely yes
Kim 2013 [53]	Definitely yes	Probably no	Definitely yes	Definitely yes	Definitely yes	Probably no	Definitely yes	Definitely no	Probably yes	Probably yes
Ko 2008 [58]	Probably no	Probably no	Definitely yes	Definitely yes	Definitely yes	Probably no	Definitely yes	Probably yes	Probably no	Probably yes
Koch 2012 [54]	Probably no	Probably no	Definitely yes	Definitely yes	Probably no	Probably no	Probably no	Probably no	Probably yes	Probably yes
Smit 2015 [56]	Probably no	Probably no	Definitely yes	Probably no	Probably no	Probably no	Probably no	Probably yes	Probably yes	Probably yes
Sunwoo 2013 [57]	Probably no	Probably no	Definitely yes	Definitely yes	Definitely yes	Probably no	Definitely yes	Probably yes	Probably yes	Probably yes
Yang 2015 [55]	Probably no	Probably no	Definitely yes	Probably no	Definitely yes	Probably no	Definitely yes	Probably yes	Probably yes	Probably yes
Non-RCTs										
Agosta 2014 [62]	Definitely no	Definitely no	Definitely yes	Probably no	Definitely yes	Probably no	Definitely yes	Probably yes	Probably no	Probably yes
Cazzoli 2015 [60]	Definitely no	Definitely no	Definitely yes	Probably no	Probably no	Probably no	Probably no	Probably no	Probably no	Probably no
Hopfner 2015 [61]	Definitely no	Definitely no	Definitely yes	Probably no	Probably no	Probably no	Probably no	Probably yes	Probably yes	Probably yes
Làdavas 2015 [63]	Definitely no	Definitely no	Definitely yes	Definitely yes	Definitely yes	Probably no	Definitely yes	Probably yes	Probably yes	Probably yes

*Defined as less than 10% loss to outcome data or difference between groups less than 5% and those excluded are not likely to have made a material difference in the effect observed.
RCTs: randomized controlled trials. Non-RCTs: non-randomized controlled trials, including quasi-RCTs.
All answers as: definitely yes (low risk of bias), probably yes, probably no, definitely no (high risk of bias).

3.4 Outcomes

Synthesized results from randomized controlled trials

Overall USN measured by Star Cancellation Test

Results from six RCTs [51-55, 57] comparing non-invasive brain stimulations with sham failed to show a benefit in overall USN measured by Star Cancellation Test (SMD -0.51, 95% CI -1.87, 0.85; p = 0.46; I^2=90%) (Figure 4). Results were consistent regardless the type of non-invasive brain stimulations: TBS with three RCTs [52,54,55] (SMD -1.61, 95% CI -4.28, 1.06; p = 0.24; I^2=93%); dual-tDCS with one RCT [57] (SMD -0.12, 95% CI -0.99, 0.76; p = 0.79; I^2=not applicable); and 1Hz rTMS with two RCTs [51,53] (SMD 0.57, 95% CI -2.95, 4.10; p = 0.75; I^2=95%) (Figure 4). Certainty in evidence was rated down to very low because of imprecision, inconsistency, and risk of bias, due to the studies were ranked as high risk of bias for both allocation sequence and allocation concealment (Table 4, Figure 2).

Table 4 - GRADE evidence profile for RCTs: non-invasive brain stimulations for unilateral spatial neglect after stroke.

Quality assessment						Illustrative comparative risks (95% CI)		Certainty in estimates OR Quality of evidence
						Assumed risk	**Corresponding risk**	
No of participants (studies) *Range follow-up Time in weeks*	*Risk of bias*	*Inconsistency*	*Indirectness*	*Imprecision*	*Publication bias*	**Sham**	**Non-invasive brain stimulations**	
Overall USN measured by Star Cancellation test								
116 (6) Immediately post intervention-4 weeks	Serious limitation[1]	Serious limitation[2]	No serious limitation[3]	Serious limitation[4]	Undetectable	The mean in change in USN measured by Star Cancellation test was 45.29 (SD 5.94)*	The std. mean in changes in USN measured by Star Cancellation test in the intervention group was on average 0.51 fewer (1.89 fewer to 0.88 more)	Very low
Overall USN measured by Line Bisection Test								
107 (5) Immediately post intervention-1 month	Serious limitation[1]	Serious limitation[2]	No serious limitation[3]	No serious limitation	Undetectable	The mean in change in USN measured by Line Bisection Test was 35.79 (SD 18.65)*	The std. mean in changes in USN measured by Line Bisection Test in the intervention group was on average 2.33 fewer (3.54 fewer to 1.12 fewer)	Low
Overall USN measured by Motor Free Visual Perception Test								
38 (2) 2-4 weeks	Serious limitation[1]	No serious limitation	No serious limitation	No serious limitation	Undetectable	The mean in change in USN measured by Motor Free Visual Perception Test was 16.9 (SD 2.1)**	The std. mean in changes in USN measured by Motor Free Visual Perception Test in the intervention group was on average 1.46 more (0.73 more to 2.20 more)	Moderate
Overall USN measured by Albert test and Line crossing test								
50 (2) 4 weeks	Serious limitation[1]	Serious limitation[2]	No serious limitation	No serious limitation	Undetectable	The mean in change in USN measured by Albert test and Line crossing test was 27.33 (SD 4.55)**	The std. mean in changes in USN measured by Albert test and Line crossing test in the intervention group was on average 1.01 more (1 fewer to 3.02 more)	Low

SD = standard error; std. = standardized

*Baseline risk estimates for overall USN come from control arm of Fu 2015 [52] study (lowest risk of bias trial in the meta-analysis).

**Baseline risk estimates for overall USN come from control arm of Cha 2016 [51] study (newest trial in the meta-analysis).

[1]The majority of the studies were ranked as high risk of bias for both allocation sequence and allocation concealment.

[2]There was a substantial heterogeneity ($I^2 > 70\%$).

[3]There was no substantially difference related to the mean age and eligibility criteria throughout the six included studies.

[4]95% CI for absolute effects include clinically important benefit and no benefit.

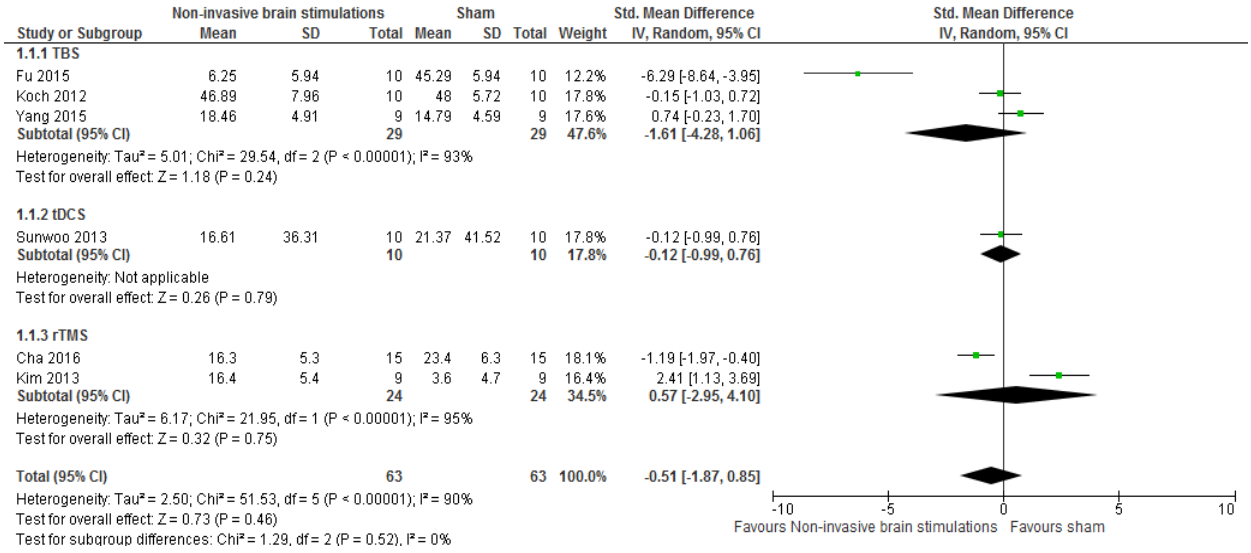
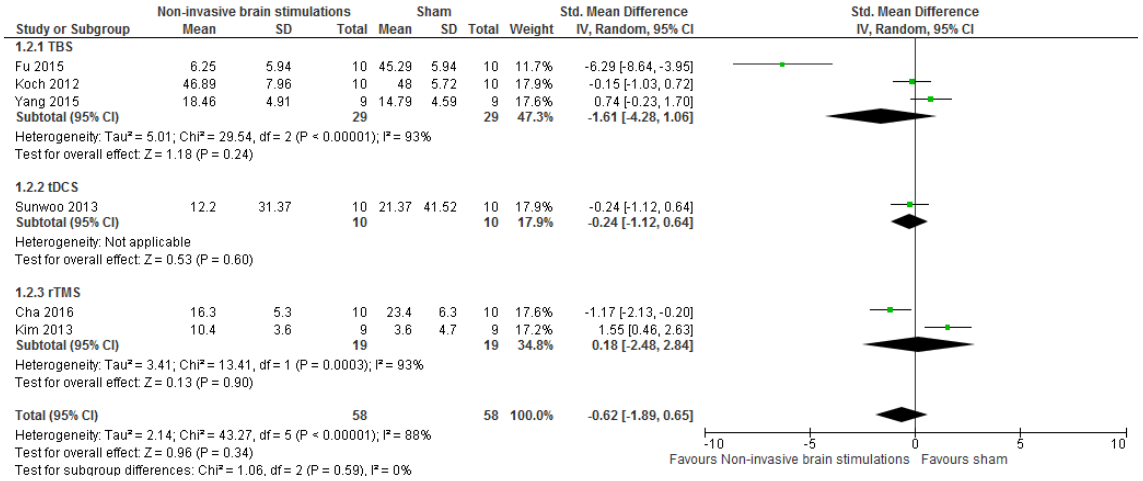


Figure 4 - Meta-analysis on overall USN measured by Star Cancellation test.

A sensitivity analysis from the same RCTs [51-55, 57] using 10Hz rTMS [53] and single-tDCS [57] yielded results that were also consistent with the primary analysis and fail to show a difference in the effects of non-invasive brain stimulations compared to sham (SMD -0.62, 95% CI -1.89, 0.65; p = 0.34; I^2=88%) (Appendix Figure 1).



Appendix Figure 1 - Sensitivity analysis on overall USN measured by Star Cancellation test using 10 Hz rTMS and single-mode tDCS.

Overall USN measured by Line Bisection Test

Results from five RCTs [51-53, 55, 57] comparing non-invasive brain stimulations with sham suggested a benefit in overall USN measured by Line Bisection Test (SMD -2.33, 95% CI -3.54, -1.12; p = 0.0002; I^2=81%) (Figure 5). Results were inconsistent analyzing the data by type of non-invasive brain stimulations: TBS with two RCTs [52,55] (SMD -3.08, 95% CI -6.54, 0.38; p = 0.08; I^2=90%); and dual-tDCS with one RCT [57] (SMD -0.66, 95% CI -1.56, 0.25; p = 0.15; I^2=not applicable); except by 1Hz rTMS with two RCTs [51,53] that yielded results that were consistent with the overall meta-analysis (SMD -2.33, 95% CI -3.54, -1.12; p < 0.0002; I^2=81%) (Figure 5). Certainty in evidence was rated down to low because of inconsistency, and risk of bias, due to the studies were ranked as high risk of bias for both allocation sequence and allocation concealment (Figure 2, Table 4).

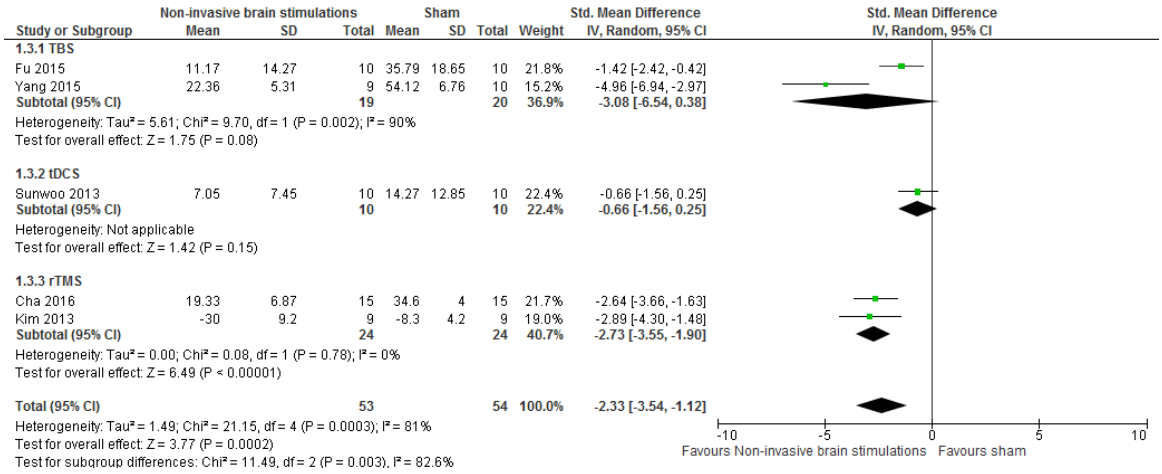
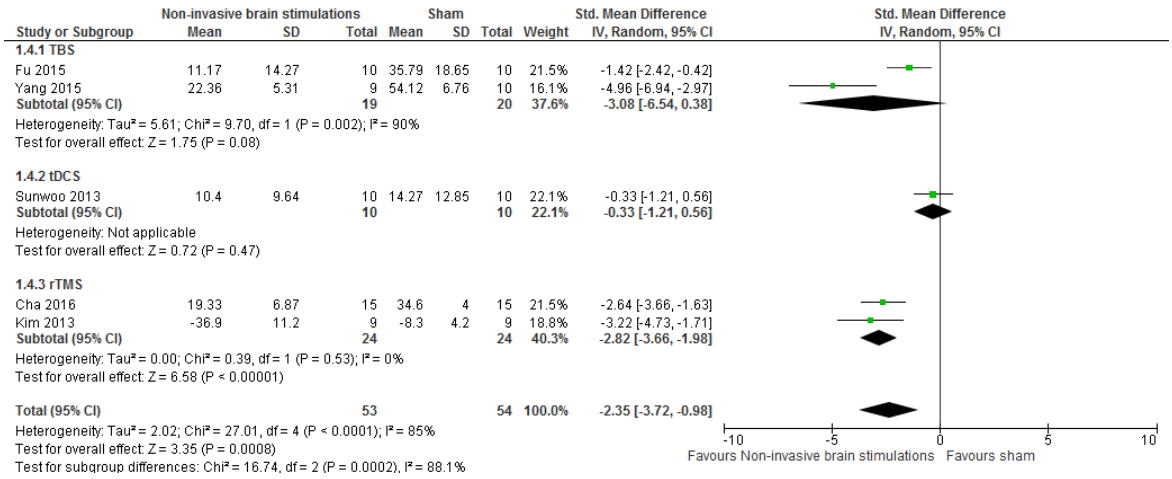


Figure 5 - Meta-analysis on overall USN measured by Line Bisection Test.

A sensitivity analysis from the same RCTs [51-53, 55, 57] using 10Hz rTMS [Kim 2013] and single-tDCS [57] yielded results that were also consistent with the primary analysis and suggested a difference in the effects of non-invasive brain stimulations compared to sham (SMD -2.35, 95% CI -3.72, -0.98; p = 0.002; I^2=85%) (Appendix Figure 2).



Appendix Figure 2 - Sensitivity analysis on overall USN measured by Line Bisection test using 10 Hz rTMS and single-mode tDCS.

Overall USN measured by Motor Free Visual Perception Test

Results from two RCTs [51,53] comparing non-invasive brain stimulations with sham suggested a benefit in overall USN measured by Motor Free Visual Perception Test with 1 Hz (SMD 1.46, 95% CI 0.73, 2.20; p < 0.0001; I^2=0%). However, in the subgroup analysis of 10 Hz there was no statistically significant difference (SMD 0.97, 95% CI -0.02, 1.96; p = 0.06; I^2=not applicable) (Figure 6). Certainty in evidence was rated down to moderate because of risk of bias, due to the studies were ranked as high risk of bias for both allocation sequence and allocation concealment (Figure 2, Table 4).

Overall USN measured by Albert test and Line crossing test

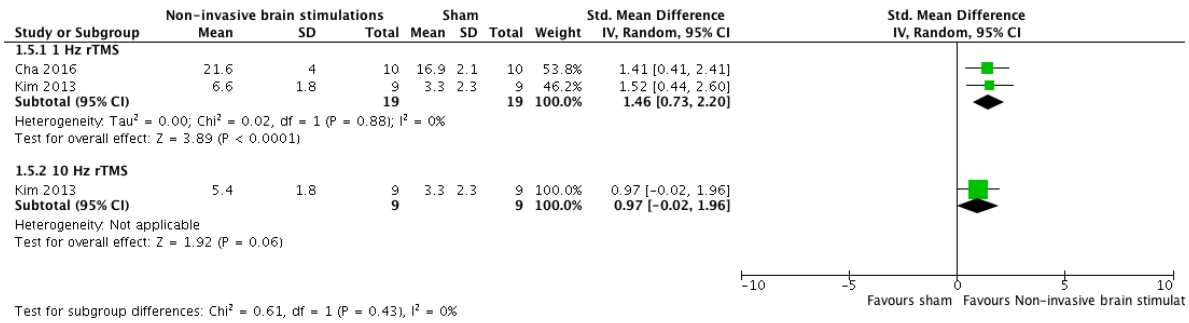


Figure 6 - Meta-analysis on overall USN measured by Motor Free Visual Perception Test.

Results from two RCTs [51,54] comparing non-invasive brain stimulations with sham failed to show a benefit in overall USN measured by Albert test and Line crossing test (SMD 1.01, 95% CI -1.0, 3.02; p =0.32; I^2=90.2%) (Figure 7). However, in the subgroup analysis with the use of 1 Hz rTMS we found a statistically significance difference compared to sham (SMD 2.04, 95% CI 1.14, 2.95; p <0.00001; I^2=not applicable). Regarding the use of TBS, there was no benefit compared to sham (SMD -0.01, 95% CI -0.89, 0.87; p =0.98; I^2=not applicable). Certainty in evidence was rated down to low because of inconsistency, and risk of bias, due to the studies were ranked as high risk of bias for both allocation sequence and allocation concealment (Figure 2, Table 4).

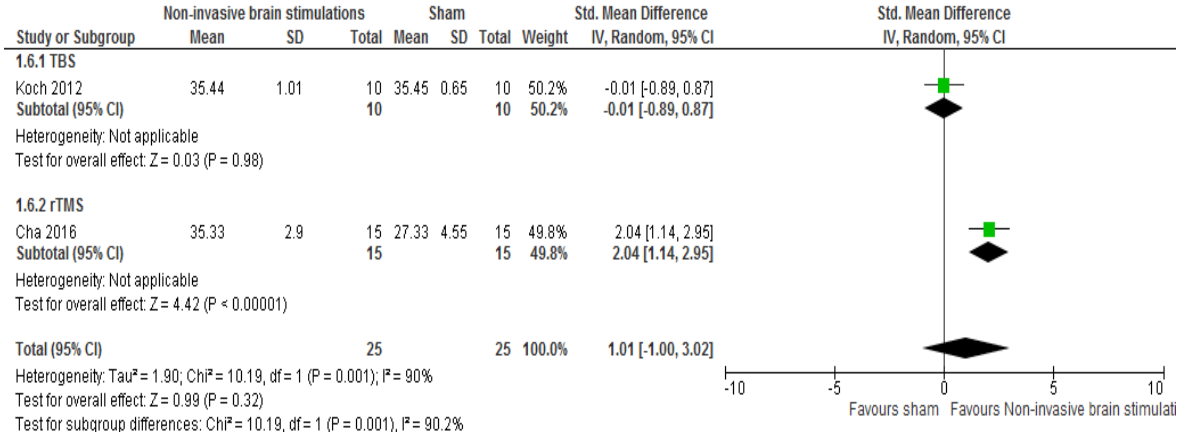


Figure 7 - Meta-analysis on overall USN measured by Albert test and Line crossing test.

<u>Other outcomes: daily life functions and adverse events</u>

Only Kim 2013 [53] reported on daily life functions with higher mean in the 10 Hz rTMS group compared to both sham and 1 Hz rMTS groups; however there was only a statistically significance difference favoring 10 Hz rTMS group compared to sham (SMD 1.83, 95% CI 0.68, 2.97; p =0.002; I^2=not applicable). Làvadas 2015 [63] was the only study that reported on adverse events, no significant adverse effect of

tDCS were reported, except only a few cases of minimal irritation of the skin beneath the electrodes

None of the included studies reported on the following outcomes: disability in neurological and functional abilities, balance, depression or anxiety; evaluation of poststroke fatigue, quality of life, and death.

Synthesized results from non-RCTs

The non-RCTs did not report data in a usable way to allow any statistical analysis.

4 DISCUSSION

4.1 Main findings

Based on pooled data from six randomized trials with 116 participants, we found evidence for a benefit in overall USN with non-invasive brain stimulation, especially with the use of rTMS in comparison to sham (Figures 5, 6 and 7). The evidence is from moderate-quality evidence because of risk of bias, due to the studies were ranked as high risk of bias for both allocation sequence and allocation concealment (Figure 2, Table 4). Non-RCTs studies provide no evidence suggesting that future trials should adhere to CONSORT guidelines to ensure clarity and reproducibility in the reporting of methods.

We presented the results of overall USN in a forest plot, which showed a statistically significant difference between the non-invasive brain stimulations and sham in the following tests: Line Bisection Test, Motor Free Visual Perception Test, and Albert test and Line crossing test. Nevertheless, the study also showed a non-significant difference between the non-invasive brain stimulations and sham on the Star Cancellation test.

Several non-invasive brain stimulations have been explored to determine whether some of these techniques might be useful in promoting recovery from USN after stroke. In three of four meta-analysis, rTMS was responsible for the improvement of overall USN, revealing that an electric current is an effective strategy for generating lasting promising effects in the brain. Unfortunately, we did not find any significant TBS or tDCS effects compared to sham procedures.

4.2 Strengths and limitation

Strengths of our review include a comprehensive search; assessment of eligibility, risk of bias, and data abstraction independently and in duplicate; assessment of risk of bias that included a sensitivity analysis addressing loss to follow-up; and use of the GRADE approach in rating the certainty of evidence for each outcome. Furthermore, there were no language restrictions and translations of non-English trials were obtained wher- everpossible.

The primary limitation of our review is the low certainty consequent on study limitations. We identified a small number of RCTs with a modest number of participants resulting wide confidence intervals. The total number of participants was relatively very low (RCTs n=278, non-RCTs n=94) due to the small sample sizes of individual trials, which led to downgrading the quality of evidence in some instances because underpowered trials are likely to have a greater degree of imprecision.

Moreover, selection bias and unblinding were substantial. Other limitations of this review were the fact of having insufficient number of included studies to allow the complete statistical analysis that we had planned. We were not able to assess publication bias because there were less than 10 eligible studies addressing the same outcome in a meta-analysis. We also planned to perform subgroup analyses according to the characteristics of: stroke type, type of stimulation, type of frequency, and comparators (type of control intervention: pharmacological therapy versus non-pharmacological). However, we also were not able to conduct these analyses because they did not meet our minimal criteria, which were at least five studies available, with at least two in each sub-group.

Although this review presents several limitations, the issue is whether one should dismiss these results entirely, or consider them bearing in mind the limitations. The latter represent our view of the matter.

4.3 Relation to prior work

The research question we investigated in our review has been addressed before from different perspectives, using our population of interest but with different intervention (i.e., pharmacological intervention) [7]; or investigating either the intervention or the control arms explored in this review, but with different population (e.g., idiopathic Parkinson's disease (IPD) [48]; panic disorder in adults [64]; or amyotrophic lateral sclerosis or motor neuron disease [13]).

The previous Cochrane review [7] that evaluated the effects of pharmacological interventions for USN after stroke concluded with uncertainty as to whether comparison of different pharmacological interventions (rivastigmine, transdermal nicotine) showed an important effect on either the ability of people to recognize their paralyzed limb or independence in daily life functions after stroke, because the results were imprecise and included studies that did not report most of the predefined outcomes (i.e, falls, balance, depression or anxiety, post-stroke fatigue, and quality of life), in addition to the small sample size and methodological limitations.

Another two Cochrane reviews [21,49] evaluated the effect of tDCS in people after stroke, but not in comparison with rTMS, instead of it the authors compared tDCS with placebo, sham tDCS, no intervention or conventional motor rehabilitation. The first review [49] authors found evidence of effect regarding activities of daily living performance at the end of the intervention period and at the end of follow up. However, the results did not persist in a sensitivity analysis including only trials of good

methodological quality. In the second review [21] the authors found that there were no studies examining the effect of tDCS on cognition in stroke patients with afasia.

Another Cochrane review [22] which addressed the use of rTMS compared to sham treatment or other conventional treatment for improving function after stroke revealed that rTMS treatment was not associated with improved activities of daily living nor had a statistically significant effect on motor function.

Three additional Cochrane reviews also discussed the effects of both tDCS [48] and rTMS [13,64], but in different populations - in Parkinsonism [48], in patients with amyotrophic lateral sclerosis or motor neuron disease [13], and in adults with panic disorder [Li 2014]. All reviews [13,48,64] suffered from poor methodological quality, imprecision, and hence low confidence in the estimate of the true effect to draw a consistent conclusion on the effects of non-invasive brain stimulations.

4.4 Implications

Moderate-quality evidence shows that rTMS, with 1 Hz, is more efficacious compared to sham for unilateral spatial neglect after stroke measured by Motor Free Visual Perception Test. Furthermore, low-quality evidence also suggests a benefit of non-invasive brain stimulation, particularly with the use of rTMS, for overall USN measured by Line Bisection Test, Albert test and Line crossing test. Future trials should adhere to CONSORT guidelines to ensure clarity and reproducibility in the reporting of methods.

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Non-invasive brain stimulations for unilateral spatial neglect after stroke: a systematic review and meta-analysis of randomized and non-randomized controlled trials

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