Non-invasive brain stimulation in rehabilitation of hemi-spatial neglect after stroke

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Abstract

Background: Non-invasive brain stimulation can modulate neural processing within the motor cortex and thereby might be beneficial in the rehabilitation of hemi-spatial neglect after stroke.

Methods: We review the pertinent literature regarding the use of transcranial direct current stimulation and transcranial magnetic stimulation in order to facilitate recovery of hemi-spatial neglect after stroke.

Results: 20 controlled trials (including 443 stroke patients) matched our inclusion criteria.

Methodology and results of each study is presented in a comparative approach. Current data seem to indicate a better efficiency of repetitive transcranial magnetic stimulation, compared to transcranial direct current stimulation.

Conclusions: Non-invasive brain stimulation has the potential to facilitate recovery of hemi-spatial neglect after stroke, but until today there are not enough data to claim its routine use.

Key words: repetitive transcranial magnetic stimulation, transcranial direct current stimulation, stroke, hemi-spatial neglect

1. Introduction

Stroke is the number one cause of long-term disability in adults worldwide.¹ A particularly disabling syndrome in these patients is hemi-spatial neglect. This syndrome is defined as the failure to detect, respond or orient towards stimuli located in the hemi-body and/or hemi-space contralateral to the lesioned hemisphere.² Generally, hemi-spatial neglect is associated with unfavorable post-stroke recovery. Patients that suffer from this syndrome show slower functional progress during rehabilitation and need longer hospitalization times.³ Hemi-spatial neglect is also an independent predictor of limited post-stroke functional independence⁴ and lower likelihood of being discharged home.⁵ Therefore, the development of innovative interventions, supporting the elimination of this syndrome, is urgently needed. Repetitive transcranial magnetic stimulation and transcranial direct current stimulation are innovative techniques that can modulate neural processing within the cortex.^{6,7} Both techniques have the potential to antagonize maladaptive neuroplasticity after a stroke and support recovery of the neglect syndrome.⁸ This paper reviews the available data of these non-invasive approaches in order to facilitate recovery of hemi-spatial neglect.

1.1. Hemi-spatial neglect

The prevalence of hemi-spatial neglect in acute stroke ranges from 30% to 81%.^{9,10,11} The neglect syndrome is most frequently associated with neural damage involving the temporal, parietal and occipital lobes, the basal ganglia and thalamus.¹² Generally, hemi-spatial neglect occurs more frequent, more severe and more persistent after right than after left hemispheric lesions.^{11,12} The pathophysiology of the syndrome is linked to a dysfunction of cortical networks within the right hemisphere, involving the posterior parietal cortex, which play a dominant role in visuospatial attention. Therefore, damage within the right hemisphere often induces neurological disorders characterized by hemi-spatial neglect.^{2,13}

A theory to explain the existence of hemi-spatial neglect is the interhemispheric rivalry model. It describes reciprocally interactive inhibitory processes exerted by both hemispheres towards one another via the corpus callosum.¹⁴ In the healthy brain there is an outweighed balance between both hemispheres regarding reciprocal inhibition and attention is deployed within the entire extra-corporal space with each hemisphere attending the contralateral space. After unilateral brain lesion, this in-between hemispheric balance is disrupted, e.g. the contralesional hemisphere is disinhibited and therefore enhanced, what then again may cause stronger inhibition towards the ipsilesional hemisphere. Clinically, a shift of spontaneous spatial attention away from midline towards the ipsilesional side may occur, what leads to an avoidance of the contralesional hemi-space and at the same time increased exploration of the ipsilesional hemi-space.^{15,16} This theory received support from several studies. A functional magnetic resonance imaging (fMRI) longitudinal study demonstrated that spatial attention deficits in neglect after right frontal damage correlate with abnormal activation of structurally intact dorsal and ventral parietal regions.¹⁷ The recovery from neglect correlates with restoration and rebalance of neural activation within these regions.¹⁷ A TMS study demonstrated an increase of functional connectivity between the contralesional posterior parietal cortex and the contralesional primary motor cortex in stroke subjects with hemi-spatial neglect.¹⁸ Amelioration of hemi-spatial neglect was accompanied by a normalization of enhanced connectivity between the posterior parietal and primary motor cortices of the unaffected hemisphere.¹⁸ Despite its limitations, the theory of interhemispheric imbalance and rivalry provides the theoretical framework for the use of non-invasive brain stimulation techniques in the rehabilitation of hemi-spatial neglect after stroke.

1.2. Non-invasive brain stimulation

Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are non-invasive brain stimulation techniques.^{6,7} Both techniques have

been used to improve clinical symptoms in neglect syndromes.²⁰⁻²³ The rationale for their application in neglect syndromes after brain damage is the fact that tDCS and rTMS either facilitate or inhibit cortical excitability and thereby neural processing within the stimulated brain areas for time periods outlasting the stimulation period.^{6,7} Within the theoretical framework of interhemispheric rivalry postulating an “overactive” contralesional hemisphere and a “suppressed” ipsilesional hemisphere, the application of non-invasive brain stimulation may outbalance cortical excitability in between both hemispheres by either facilitation of the ipsilesional hemisphere or, alternatively, inhibition of the contralesional hemisphere.⁸ TDCS applies a low-intensity current via two electrodes (anode and cathode) placed on the scalp. One of the electrodes is positioned over the target area (active electrode), the other (reference electrode) over another cranial or extracranial position.²⁴ Anodal stimulation (anode over the target area) induces a depolarization of cortical neurons and thereby an increase of cortical excitability. Cathodal stimulation (cathode over the target area) induces hyperpolarization and decreases cortical excitability.²⁵ During transcranial magnetic stimulation (TMS) a magnetic coil is placed on the scalp overlying the cortical target area. Discharging the electromagnetic coil induces a current flow within the cortex. Depending on frequency, repetitive TMS (rTMS) may increase (representing long term potentiation) or decrease (representing long term depression) motor cortical excitability. High-frequency rTMS ($\geq 5\text{Hz}$), intermittent theta burst stimulation (iTBS) and paired-pulse stimulation (inter-stimulus interval 1.5ms) cause an increase, low-frequency rTMS (1Hz), continuous theta burst stimulation (cTBS) and paired-pulse stimulation (inter-stimulus interval 3ms) a decrease of the motor cortex excitability.²⁶ Still, recently studies indicate that the responses to excitatory and inhibitory non-invasive brain stimulation protocols are highly variable between individuals.^{27,28} The individuals factors determining the responsiveness of cortical excitability are not completely understood.

2. Methods

2.1. Studies included

We reviewed the PubMed database prior to 30/05/2017 for papers reporting on the use of non-invasive brain stimulation in rehabilitation of hemi-spatial neglect in stroke. The search terms “transcranial direct current stimulation” and “neglect” and “repetitive magnetic transcranial stimulation” and “neglect” were used. Studies matching the following criteria were included: (1) human-studies, (2) prospective studies, (3) diagnosis of stroke and hemi-spatial neglect, (4) tDCS or/and rTMS used as intervention for improving hemi-spatial neglect (5) assessment of hemi-spatial neglect before and after the intervention, (6) placebo controlled study or study with at least two experimental groups.

2.2. Outcomes

The primary outcome was hemi-spatial neglect. Secondary outcomes were (1) stimulation parameters (technique used - rTMS/tDCS, stimulated hemisphere - ipsilesional/contralesional/bilateral, stimulated areas - P3/P4/P5/P6 of international electrode placement system representing posterior parietal cortex of the left (P3/P5) and of the right (P4/P6) hemisphere, stimulation duration, stimulation intensity), (2) characteristics of subjects included (time since stroke, stroke etiology – ischemic/hemorrhagic, stroke location – cortical/subcortical, affected hemisphere – right/left), and (3) study design (crossover/parallel groups, presence/absence of follow up, presence/absence of additional intervention).

2.3. Data analysis

Effect size and the 95% confidence intervals were calculated for each study to evaluate the efficiency of non-invasive brain stimulation for recovery from hemi-spatial neglect. The effect size was calculated either based on means and SD of repeated measures (pre, post), or based on means and SD of pre-post differences. For studies that used more than one hemi-spatial neglect assessments, effects size and the confidence intervals were calculated for each

assessment. Finally means were calculated for each study, a forest plot was constructed. For interpretation, the Cohen definition of effect size was used ($d = 0.2$ “small”, $d = 0.5$ “medium”, $d = 0.8$ “large”). Effect size calculation gives the opportunity to compare the effectivity of treatments reported in in different trials. However, it should keep in mind that comparing effect size (e.g. between studies evaluating various therapies) is only useful if the manner in which these effects sizes are calculated, are comparable. That is, studies that differ substantially regarding design or used methodology could complicate the comparison of effect sizes and could, therefore, easily lead to false conclusions.²⁹

3. Results

3.1. Transcranial direct current stimulation

A total of 8 studies were found that tested the effect of tDCS to improve hemi-spatial neglect after stroke.^{21,23,30-35} A total of 146 stroke subjects were included. Studies were heterogeneous regarding the study population included and the methods used (Table 1). Serious adverse events were not described.

3.1.2. Facilitatory tDCS over the ipsilesional hemisphere

Five controlled trials tested the effect of anodal tDCS over the ipsilesional hemisphere. One study revealed a significant improvement of hemi-spatial neglect with 2mA anodal tDCS, compared to sham treatment.³² The remaining studies showed a significant improvement with 1mA or 2mA anodal tDCS (compared to sham stimulation), but only for some of the performed tests.^{21,31,34,35}

3.1.3. Facilitatory tDCS over the contralesional hemisphere

Only one study investigated the efficiency of 1mA anodal tDCS over the contralesional hemisphere.³⁴ The results showed no treatment-related improvement of hemi-spatial neglect, compared to sham tDCS.

3.1.4. Inhibitory tDCS over the contralesional hemisphere

Three studies probed the effect of cathodal tDCS over the contralesional hemisphere in comparison to sham stimulation. Two of them revealed significant treatment-related positive effects of real 2mA³⁵ and real 1mA³⁴ tDCS, again only for a sub-group of hemi-spatial neglect tests performed. One study detected a deteriorating effect of real 2mA tDCS.³²

3.1.5. Bilateral tDCS

Four controlled studies tested the efficiency of bilateral tDCS. Two studies revealed a significant improvement of hemi-spatial neglect with 1mA bilateral tDCS, compared to sham stimulation.^{21,30} One study showed a significant improvement with 1.5-2mA bilateral tDCS combined with optokinetic treatment in subacute stroke, but only in a sub-set of tests performed²³ One study found no treatment-related effect of 2mA bilateral tDCS on improvement of chronic hemi-spatial neglect.³³

3.1.6. Comparison of different protocols

Four trials compared different tDCS protocols to improve hemi-spatial neglect in stroke. Three of them compared anodal tDCS over the ipsilesional hemisphere with cathodal tDCS over the contralesional hemisphere. One of them found a better recovery with anodal tDCS.³² Two found no significant treatment-related effects on hemi-spatial neglect.^{34,35} One study compared anodal tDCS over the ipsilesional hemisphere with bilateral tDCS and found a significant greater improvement with bilateral tDCS.²¹

3.1.7. Summary

Despite the very limited amount of data available today, the use of tDCS to improve hemi-spatial neglect after stroke is a promising approach. Anodal and bilateral tDCS application appears to be more effective than cathodal tDCS (Table 2). Future studies should differentially probe different tDCS protocols in rehabilitation of hemi-spatial neglect. Larger patient cohorts and long-term effects should be evaluated.

3.2. Repetitive transcranial magnetic stimulation

12 controlled studies investigated the effect of rTMS on recovery of hemi-spatial neglect.^{19,20,36-45} These studies included a total of 297 stroke subjects. There is large variability of methods and of subjects included among these trials (Table 3). Any study describes serious adverse events.

3.2.1. Facilitatory rTMS over the ipsilesional hemisphere

Two placebo controlled studies investigated the efficiency of facilitatory rTMS applied over the ipsilesional hemisphere.^{40,44} Both found a significant improvement with 10Hz rTMS (compared to sham), but one of them only in a sub-set of tests.⁴⁰

3.2.2. Inhibitory rTMS over the contralesional hemisphere

Five controlled studies tested the effect of continuous theta burst stimulation over the contralesional hemisphere on improvement of hemi-spatial neglect.^{19,37,38,42,44} Four studies found a significant greater improvement with real rTMS (compared to control) in all tests performed, one study in only a sub-set of tests.³⁶ Eight studies investigated inhibitory 1Hz rTMS^{37,39-41,43-45} and 0.5Hz rTMS²⁰ over the contralesional hemisphere. Five of them found a significant greater improvement with real rTMS in each assessment performed.^{20,37,39,43,44} Two studies found a greater improvement with rTMS in only a sub-set of tests performed.^{40,45} One study showed no supportive effect of rTMS.⁴¹

3.2.3. Comparison of different protocols

Only two studies compared the efficiency of different rTMS protocols in the rehabilitation of hemi-spatial neglect. 10Hz rTMS over the ipsilesional hemisphere was compared to 1Hz rTMS⁴⁰ or cTBS⁴⁴ over the contralesional hemisphere. The results indicate the best improvement with cTBS and the smallest improvement with 1Hz rTMS.

3.2.4. Summary

Today, quite large evidence for the effectiveness of rTMS to improve hemi-spatial neglect after stroke exists. The major part of available data implies a positive influence of rTMS on recovery from hemi-spatial neglect symptoms. Based on currently data, cTBS is the most effective stimulation. In contrast, conventional rTMS over the contralesional hemisphere appears to be less efficient (Table 2). Future studies should compare facilitatory and inhibitory rTMS protocols within larger study cohorts and include long-term follow up investigations.

4. Discussion

This review analyzed data from 20 controlled intervention trials including a total of 443 stroke patients with hemi-spatial neglect after stroke. Collectively the data suggests a positive effect of non-invasive brain stimulation to improve hemi-spatial neglect in patients with stroke, but the current evidence is too small for a routine use in rehabilitation. This is caused by an overall limited number of patients included, heterogeneity of stimulation protocols and assessment regimen and a very small proportion of studies providing a long-term follow up.

4.1. Stimulation protocols

Inhibitory rTMS over the parietal lobe of the contralesional hemisphere is the most widely used stimulation protocol in rehabilitation of hemi-spatial neglect after stroke. Its efficiency

was tested in 170 patients. Other rTMS protocols were less frequently applied (between 13 and 48 patients). In the future more comparative studies should be designed. In particular, effect size of inhibitory versus facilitatory rTMS and tDCS over the contralesional and ipsilesional hemisphere should be compared.

Bilateral (ipsi- and contralesional) stimulation to improve hemi-spatial neglect after stroke has been used only via tDCS. Future studies should evaluate the potential of bihemispheric rTMS or a combination of rTMS and tDCS. Such stimulation protocols have already been successfully tested in motor rehabilitation after stroke.^{23,46-48}

Currently data indicates (1) a stimulation method dependent efficiency and (2) a stimulation protocol dependent efficiency. Figure 2 demonstrates that rTMS appears to be more effective than tDCS in improving hemi-spatial neglect. In addition, inhibitory stimulation of the contralesional hemisphere is the least efficient stimulation protocol. In contrast, bilateral tDCS and cTBS show the highest efficiency. However, more data are needed to allow definite conclusions about the efficiency of diverse protocols.

4.2. Study design

Current studies investigating rTMS and tDCS to improve hemi-spatial neglect differ in many relevant aspects: (1) number of patients included (tDCS: 19 participants on average per study, rTMS: 25 patients on average per study), (2) the amount of stimulation sessions (tDCS: 8 sessions on average per study, rTMS: 16 sessions on average per study) and (3) long-term follow up investigation (tDCS: only one study with follow-up over 5 days, rTMS: 7 studies with follow-up up to 6 weeks). Thus, more data are needed about long-term effects (over several months) of the repetitive application of non-invasive brain stimulation for improving the hemi-spatial neglect after a stroke.

Only a small part of available studies (four studies evaluation tDCS, and four studies evaluating rTMS) mention to use double-blinded study design. However, a blinding of both patients and investigators is a critical point in the interpretation of the results. Thus, in the future, more double-blinded studies are needed to understand correctly the effects of non-invasive brain stimulation on hemi-spatial neglect after a stroke. Furthermore, the essential limit of the mostly present studies is absence of neuronavigated techniques to maintain the adequate coil position during the treatment. In the majority of studies the international 10–20 EEG System was used.

4.3. Patient characteristics

At present non-invasive brain stimulation techniques have mostly been applied in subacute and chronic stroke survivors with hemi-spatial neglect. Future trials should investigate the efficiency of rTMS and tDCS in larger study cohorts of acute stroke subjects.

In about one half of all trials no information about lesion location within the affected hemisphere had been provided. This is a flaw and should change in future studies to allow a proper judgment about lesion location and distribution and its relationship to the effectiveness of brain stimulation techniques. Until today, about three times more stroke subjects with a cortical involvement, as compared to pure subcortical tissue damage, underwent tDCS or rTMS to enhance recovery from neglect.

About a quarter of trials did not provide information regarding stroke etiology. The remaining trials enrolled nearly two times more patients with ischemic stroke than patients with hemorrhagic stroke. Stroke etiology, however, may be relevant as the effectiveness of rTMS and tDCS to overcome hemi-spatial neglect may differ in ischemic and hemorrhagic stroke, as it may do in different lesion locations and distributions within the brain.

5. Limitations

The studies included in our review shows a large variability of the study population (time from stroke, stroke etiology, stroke location), stimulation protocol (tDCS/rTMS, intensity, duration, number of sessions, stimulated hemisphere, stimulated area), assessments, study design (parallel groups/crossover, with/without an additional intervention), as well as methodological quality (blinding, sham condition technique). It should mean limitations for the comparison of effect sizes.

Definitions

Acute stroke	within 2 weeks from symptom onset
Subacute stroke	2 weeks to 3 months from symptom onset
Chronic stroke	more than 3 months from symptom onset

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Figure and table legends

Table 1: Overview of studies investigating tDCS for recovery of hemi-spatial neglect.

mA = milliampere; na = not available, not applicable; tDCS = transcranial direct current stimulation

Reference	Number of participants / sex	Time since stroke	Stroke etiology / lesion location / affected hemisphere	Study design / blinding	Treatment	Number of tDCS sessions / Evaluations	Results (group*time effect / performed tests)
Turgut et al., 2016	32 / 21 males, 11 females	25 ± 17 days	na / na / 20 right hemisphere, 12 left hemisphere	parallel groups (16+16) / no blinding	(1) 1.5-2mA bilateral tDCS (20 min) over P3,P4 in combination with an optokinetic task (2) no treatment	10 sessions / evaluations: T1 5 days before treatment, T2 immediately before treatment, T3 immediately after treatment, T4 5-6 days after treatment	1.5-2mA bilateral tDCS combined with an optokinetic task significantly better than no intervention: spontaneous body orientation, Clock Drawing Test, line bisection, Apples Cancellation Task - exocentric neglect No treatment significantly better than 1.5-2mA bilateral tDCS combined with an optokinetic task: Apples Cancellation Task - allocentric neglect
Ko et al., 2008	15 / 10 males, 5 females	47 ± 18 days	10 ischemic, 5 hemorrhagic / 9 cortical, 6 subcortical / right hemisphere	crossover (15/15) / double blinding	(1) 2mA anodal tDCS (20 min) over P4 (2) sham tDCS (20 min, current turned off after 10s) over P4	1 session / evaluations: T1 before treatment, T2 immediately after treatment	2mA anodal tDCS significantly better than sham tDCS: line bisection test, shape-unstructured cancellation test no significant differences: letter-structured cancellation test
Bang et al., 2015	12 / 4 males, 8 females	6.6 ± 1.7 weeks	na / na / right hemisphere	parallel groups (6+6) / no blinding	(1) 1mA bilateral tDCS (20 min) over P3 and P4 in combination with a feedback training (30 min) (2) no tDCS in combination with a feedback training (30 min)	15 sessions / evaluations: T1 before treatment, T2 after treatment	1mA bilateral tDCS significantly better than no tDCS: motor-free visual perception, line bisection test
Sparing et al., 2009	10 / 4 males, 6 females	2.9 ± 3.5 months	na / na / right hemisphere	crossover (10/10/10/10) / no blinding	(1) 1mA anodal tDCS (10 min) over P3 (2) 1mA cathodal tDCS (10 min) over P3 (3) 1mA anodal tDCS (10 min) over P4 (4) sham tDCS (10 min, current turned off after 30s) over P4	1 session / evaluations: T1 before treatment, T2 after treatment	1mA cathodal tDCS contralesional and 1mA anodal tDCS ipsilesional significantly better than 1mA anodal tDCS contralesional and sham tDCS: line bisection task no significant differences: number of cancelled stimuli
Udavas et al., 2015	30 / 16 males, 14 females	3.0 ± 1.6 months	na / na / right hemisphere	parallel groups (11+8+11) / double blinding	(1) 2mA anodal tDCS (20 min) over P6 in combination with prism adaptation treatment (2) 2mA cathodal tDCS (20 min) over P5 in combination with prism adaptation treatment (3) sham tDCS (20 min, current turned off after 20s) over P5/P6 in combination with prism adaptation treatment	10 sessions / evaluations: T1 within the week before treatment, T2 within the week after treatment	2mA anodal tDCS significantly better than 2mA cathodal tDCS and sham tDCS: Behavioural Inattention Test sham tDCS significantly better than cathodal tDCS: Behavioural Inattention Test
Smit et al., 2015	5 / 3 males, 2 females	4.8 ± 4.4 years	2 ischemic, 3 hemorrhagic / 5 cortical / right hemisphere	crossover (5/5) / double blinding	(1) 2mA bilateral tDCS (20 min) over P3 and P4 (2) sham tDCS (20 min, current intensity increased for 30 s, and then tapered off over 30 s) over P3 and P4	5 sessions / evaluations: T1 before treatment, T2 after treatment	no significant differences: Behavioural Inattention Test
Reference	Number of participants / sex	Time since stroke	Stroke etiology / lesion location / affected hemisphere	Study design / blinding	Treatment	Number of tDCS sessions / Evaluations	Results (group*time effect / performed tests)
Sunwoo et al., 2013	10 / 4 males, 6 females	27.8 ± 60.4 months	7 ischemic, 3 hemorrhagic / 8 cortical, 2 subcortical / right hemisphere	crossover (10/10/10) / double blinding	(1) 1mA bilateral tDCS (20 min) over P3 and P4 (2) 1mA anodal tDCS (20 min) over P4 (3) sham tDCS (20 min, current intensity increased for 5 s, and then tapered off over 5 s) over P3 and P4	1 session / evaluations: T1 before treatment, T2 1 week after treatment	1mA bilateral tDCS significantly better than 1mA anodal tDCS and sham tDCS: line bisection test 1mA anodal tDCS significantly better than sham tDCS: line bisection test no significant differences: star cancellation test
Yi et al., 2016	32 / 22 males, 10 females	na	26 ischemic, 4 hemorrhagic / 27 cortical, 3 subcortical / right hemisphere	parallel groups (10+10+10) / no blinding	(1) 2mA anodal tDCS (30 min) over P4 in combination with occupational therapy (2) 2mA cathodal tDCS (30 min) over P3 in combination with occupational therapy (3) sham tDCS (30 min, current turned off after 30s) over P4 in combination with occupational therapy	15 sessions / evaluations: T1 before treatment, T2 1 week after treatment	2mA anodal tDCS and 2mA cathodal tDCS significantly better than sham tDCS: motor-free visual perception test, star cancellation test, line bisection test no significant differences: Catherine Bergego Scale

Table 2: Overview of studies investigating rTMS for recovery of hemi-spatial neglect.

aMT = active motor threshold; cTBS = continuous theta burst stimulation; na = not available, not applicable; PPC = posterior parietal cortex; rMT = resting motor threshold; rTMS = repetitive transcranial magnetic stimulation

Reference	Number of participants, sex, affected hemisphere	Time since stroke	Stroke etiology / lesion location / affected hemisphere	Study design / blinding / coil positioning techniques	Treatment	Number of rTMS sessions / Evaluations	Results (group*time effect / performed tests)
Kim et al., 2013	27 / 15 males, 12 females	15 ± 6 days	23 ischemic, 4 hemorrhagic, 23 cortical, 4 subcortical / right hemisphere	parallel groups (9+9+9) / double blinding / 10–20 EEG System	(1) 1Hz rTMS (1200 pulses 90% rMT, coil sagittally, handle posterior) over P3 (2) 10Hz rTMS (1000 pulses 90% rMT, coil sagittally, handle posterior) over P4 (3) sham rTMS (1 Hz rTMS 1200 pulses 90% rMT, coil perpendicular) over P3	10 sessions / evaluations: T1 before treatment, T2 immediately after treatment	1Hz and 10Hz rTMS significantly better than sham rTMS: Korean-Modified Barthel Index 10Hz rTMS significantly better than sham rTMS: line bisection test no significant differences: Motor-Free Visual Perception Test, star cancellation test, Catherine Bergego Scale
Olivieri et al., 2001	7 / 4 males, 3 females	16 ± 18 days	na / 5 cortical, 2 subcortical / 5 right hemisphere, 2 left hemisphere	crossover (7/7) / no blinding / MRI scan	(1) 25Hz rTMS (300 pulses 115%rMT) over P5 or P6 of the contralesional hemisphere (2) sham rTMS (coil perpendicular) over P5 or P6 of the contralesional hemisphere	1 session / evaluations: T1 before treatment, T2 after treatment	25Hz rTMS significantly better than sham rTMS: line bisection test
Cazzoli et al., 2012	24 / 17 males, 7 females	27 days	14 ischemic, 10 hemorrhagic / na / right hemisphere	parallel groups (8+8+8) / double blinding / 10–20 EEG System	(1) cTBS (801 pulses 100%rMT, coil tangentially, handle posteriorly) over P3, then sham rTMS (sham coil) over P3 (2) sham rTMS (sham coil) over P3, then cTBS (801 pulses 100% rMT, coil tangentially, handle posteriorly) over P3 (3) no rTMS	8 sessions / evaluations: T1 before treatment, T2 after treatment, T3 3 weeks after treatment	"cTBS than sham rTMS" and "sham rTMS than cTBS" significantly better than no rTMS: Catherine Bergego Scale, Vienna Test System, random shape cancellation test, two part picture test cTBS significantly better than sham rTMS: Catherine Bergego Scale, Vienna Test System, random shape cancellation test, two part picture test no significant differences: Munich reding texts
Song et al., 2009	14 / 8 males, 6 females	38 ± 15 days	6 ischemic, 8 hemorrhagic / 9 cortical, 5 subcortical / right hemisphere	parallel groups (7+7) / investigator blinded / 10–20 EEG System	(1) 0.5Hz rTMS (450 pulses 90%rMT, handle upwards) over P3 (2) no rTMS	20 sessions / evaluations: T1 2 weeks before treatment, T2 before treatment, T3 after treatment, T4 2 weeks after treatment	0.5Hz rTMS significantly better than no rTMS: line bisection test, star cancellation test
Yang et al., 2016	60 / 43 males, 17 females	42 ± 39 days	41 ischemic, 19 hemorrhagic / na / right hemisphere	parallel groups (20+20+20) / 10–20 EEG System / investigator blinded	(1) 1Hz rTMS (900 pulses 90% rMT, coil tangentially) over P5 in combination with sensory cueing (2) 1Hz rTMS (900 pulses 90% rMT, coil tangentially) over P5 (3) no treatment	10 sessions / evaluations: T1 one day before treatment, T2 immediately after treatment, T3 6 weeks after treatment	1Hz rTMS combined with sensory cueing and 1Hz rTMS significantly better than no treatment: Behavioural inattention Test no significant differences: Catherine Bergego Scale
Reference	Number of participants, sex, affected hemisphere	Time since stroke	Stroke etiology / lesion location / affected hemisphere	Study design / blinding / coil positioning techniques	Treatment	Number of rTMS sessions / Evaluations	Results (group*time effect / performed tests)
Fu et al., 2015	20 / 16 males, 4 females	19–114 days	9 ischemic, 11 hemorrhagic, 11 cortical, 9 subcortical / right hemisphere	parallel groups (10+10) / double blinding / na	(1) cTBS (600 min, 90%rMT) over P5 in combination with visuospatial scanning training (30 min) (2) sham rTMS (coil perpendicular) over P5 in combination with visuospatial scanning training (30 min)	56 sessions / evaluations: T1 before treatment, T2 after treatment, T3 4 weeks after treatment	cTBS significantly better than sham rTMS: line bisection test, star cancellation test
Koch et al., 2012	18 / na	subacute	18 ischemic / na / right hemisphere	parallel groups (9+9) / double blinding / neuronavigation, MRI scan	(1) cTBS (600 pulses 80%aMT, coil tangentially, handle downward and posteriorly) over PPC (2) sham rTMS (coil perpendicular) over PPC	20 sessions / evaluations: T1 before treatment, T2 after treatment, T3 2 weeks after treatment	cTBS significantly better than sham rTMS: Behavioral inattention Test
Yang et al., 2015	38 / 18 males, 20 females	3.1 ± 1.2 months	24 ischemic, 24 hemorrhagic / 27 cortical, 11 subcortical / na	parallel groups (9+10+9+10) / no blinding / 10–20 EEG System	(1) 1Hz rTMS (656 pulses 80% rMT) over P3 (2) 10Hz rTMS (1000 pulses 80% rMT) over P4 (3) cTBS (801 pulses 80% rMT) over P3 (4) sham rTMS (10 Hz, back of the coil facing towards the skull) (1000 pulses 80% rMT) over P4	20 sessions / evaluations: T1 2 weeks before treatment, T2 before treatment, T3 after treatment, T4 1 month after treatment	cTBS significantly better than 1Hz, 10Hz and sham rTMS: star cancellation test 1Hz and 10Hz rTMS significantly better than sham rTMS: star cancellation test 1Hz rTMS and cTBS significantly better than 10Hz and sham rTMS: line bisection test 10Hz rTMS significantly better than sham rTMS: line bisection test
Lim et al., 2010	14 / 4 males, 10 females	100 ± 152 days	9 ischemic, 5 hemorrhagic / 10 cortical, 4 subcortical / right hemisphere	parallel groups (7+7) / no blinding / 10–20 EEG System	(1) 1Hz rTMS (900 pulses 90% rMT, coil tangentially) over P5 in combination with standardized neglect therapy (2) no rTMS in combination with standardized neglect therapy	10 sessions / evaluations: T1 1 day before treatment, T2 1 day after treatment	no significant differences: Albert test, line bisection test
Cha et al., 2015	30 / 16 males, 14 females	4.0 ± 1.0 months	18 ischemic, 12 hemorrhagic / na / na	parallel groups (15+15) / double blinding / 10–20 EEG System	(1) 1Hz rTMS (1200 pulses 90% rMT) over P3 in combination with conventional therapy (30 min) (2) sham rTMS (sham coil) over P3 in combination with conventional therapy (30 min)	20 sessions / evaluations: T1 before treatment, T2 after treatment	1Hz rTMS significantly better than sham rTMS: line bisection test, Albert Test
Nyffeler et al., 2009	11 / na	7.1 ± 12.4 months	9 ischemic, 2 hemorrhagic / na / right hemisphere	parallel groups / crossover (5/5/5) / no blinding / 10–20 EEG System	(1) cTBS (801 pulses 100% rMT, coil tangentially, handle backwards) over P3 (2) sham rTMS (sham coil) over P3 (3) no rTMS	2 sessions / evaluations: T1 before treatment, T2 1 hour after treatment, T3 8 hours after treatment	cTBS significantly better than sham rTMS and no rTMS: perceived left visual targets, reaction time left
Kim et al., 2015	34 / 15 males, 19 females	19 ± 12 months	ischemic, hemorrhagic / 18 cortical, 14 subcortical / right	parallel groups (15+19) / no blinding / 10–20 EEG System	(1) 1Hz rTMS (1200 pulses 90% rMT) over P3 (10 sessions) (2) 1Hz rTMS (1200 pulses 90% rMT) over P3 (1 session)	10 sessions, 1 session / evaluations: T1 before treatment, T2 after treatment	10 sessions of 1Hz rTMS significantly better than 1 session of 1Hz rTMS: letter cancellation test, line bisection test, Ota's task

Figure 1: Positioning of the anode and of the cathode during (A) inhibitory tDCS over the contralesional hemisphere, (B) facilitatory tDCS over the ipsilesional hemisphere, and (C) bilateral stimulation.

+ = anode; - = cathode

Figure 2: Overview of effect size and 95% confidence interval for neglect outcome measures.

CL = contralesional; cTBS = continuous theta burst stimulation; Hz = Hertz; IL = ipsilesional; mA = milliampere; rTMS = repetitive transcranial magnetic stimulation; tDCS = transcranial direct current stimulation; ■,◆ = repetitive transcranial magnetic stimulation; □,◇ = transcranial direct current stimulation