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ORIGINAL RESEARCH

Noninvasive brain stimulation in rehabilitation of hemispatial neglect after stroke

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Background. Noninvasive brain stimulation can modulate neural processing within the motor cortex and thereby might be beneficial in the rehabilitation of hemispatial neglect after stroke.

Methods. We review the pertinent literature regarding the use of transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation in order to facilitate recovery of hemispatial neglect after stroke.

Results. Twenty controlled trials (including 443 stroke patients) matched our inclusion criteria. Methodology and results of each study are presented in a comparative approach. Current data seem to indicate a better efficiency of repetitive transcranial magnetic stimulation, compared to tDCS to ameliorate hemispatial neglect after stroke.

Conclusions. Noninvasive brain stimulation has the potential to facilitate recovery of hemispatial neglect after stroke, but until today, there are not enough data to claim its routine use.

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Key words: Repetitive transcranial magnetic stimulation, transcranial direct current stimulation, stroke, hemispatial neglect.

Introduction

Stroke is the number one cause of long-term disability in adults worldwide.[1] A particularly disabling syndrome in these patients is hemispatial neglect. This syndrome is defined as the failure to detect, respond, or orient toward stimuli located in the hemi-body and/or hemispace contralateral to the lesioned hemisphere.[2] Generally, hemispatial 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] Hemispatial neglect is also an independent predictor of limited post-stroke functional independence[4] 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 (rTMS) and transcranial direct current stimulation (tDCS) 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 noninvasive approaches in order to facilitate recovery of hemispatial neglect after stroke.

Hemispatial neglect

The prevalence of hemispatial 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, and the basal ganglia and thalamus.[12] Generally, hemispatial 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 plays a dominant role in visuospatial attention. Therefore, damage within the right hemisphere often

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induces neurological disorders characterized by hemispatial neglect.[2,13]

A theory to explain the existence of hemispatial neglect after brain lesion is the interhemispheric rivalry model. It describes reciprocally interactive inhibitory processes exerted by both hemispheres toward one another via the corpus callosum.[14] In the healthy brain, there is an out-weighted balance between both hemispheres regarding reciprocal inhibition, and attention is deployed within the entire extracorporal space with each hemisphere attending the contralateral space. After unilateral brain lesion, this in-between hemispheric balance is disrupted, for example, the contralesional hemisphere is disinhibited and therefore enhanced, what then again may cause stronger inhibition toward the ipsilesional hemisphere. Clinically, a shift of spontaneous spatial attention away from midline toward the ipsilesional side may occur, which leads to an avoidance of the contralesional hemispace and at the same time increased exploration of the ipsilesional hemispace.[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 hemispatial neglect.[18] Amelioration of hemispatial neglect was accompanied by a normalization of enhanced connectivity between the posterior parietal and the 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 noninvasive brain stimulation techniques in the rehabilitation of hemispatial neglect after stroke.

Noninvasive brain stimulation

rTMS and tDCS are noninvasive brain stimulation techniques.[6,7] Both techniques have been used to improve clinical symptoms in neglect syndromes.[19-22] 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 noninvasive 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.[23] 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.[24]

During 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, rTMS may increase (representing long-term potentiation) or decrease (representing long-term depression) motor cortical excitability. High-frequency rTMS (≥5 Hz), intermittent theta burst stimulation (iTBS), and paired-pulse stimulation (inter-stimulus interval 1.5 ms) cause an increase of the motor cortex excitability; low-frequency rTMS (1 Hz), continuous theta burst stimulation (cTBS), and paired-pulse stimulation (inter-stimulus interval 3 ms) cause a decrease of the motor cortex excitability.[25] However, recent studies indicate that the responses to excitatory and inhibitory noninvasive brain stimulation protocols are highly variable between individuals.[26,27] The factors responsible for the inter-individual variability of the effect of noninvasive brain stimulation on cortical excitability are not completely understood.

Methods

Studies included

We reviewed the PubMed database prior to May 30, 2017, for papers reporting on the use of noninvasive brain stimulation in rehabilitation of hemispatial neglect after 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 hemispatial neglect, (4) tDCS or/and rTMS used as intervention for improving hemispatial neglect, (5) assessment of hemispatial neglect before and after the intervention, and (6) placebo-controlled study or study with at least two experimental groups.

Outcomes

The intensity of hemispatial neglect, its change after intervention, the stimulation techniques and stimulation parameters used (rTMS or tDCS), the stimulated hemisphere (ipsilesional/contralesional/bilateral), the stimulated brain regions (P3/P4/P5/P6 of the international electrode positioning system, representing posterior parietal cortex of the left (P3/P5) or right (P4/P6) hemisphere, respectively), stimulation duration, stimulation intensity), characteristics of subjects included (time since stroke, stroke etiology – ischemic/hemorrhagic, stroke location – cortical/subcortical, affected hemisphere – right/left), and study design (crossover/parallel groups, presence/absence of follow-up, presence/absence of additional intervention) were all assessed.

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 hemispatial neglect. The effect size was calculated either based on means and SD of repeated measures (pre and post) or based on means and SD of pre–post differences. For studies using more than one hemispatial neglect assessment, effect size and confidence intervals were calculated for each assessment. Finally, means were calculated for each study and 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 provides a possibility to compare the effectivities of treatments reported in different trials. However, it should be kept in mind that comparing effect sizes (e.g. between studies evaluating various therapeutic strategies) is useful only in case the method of calculating effect size is comparable between the studies included. Studies that differ substantially regarding design or methodology could taint the comparison of effect size and therefore cause incorrect conclusions.[28]

Results

Transcanial direct current stimulation

A total of eight studies were detected. All tested the effect of tDCS to improve hemispatial neglect after stroke.[20,22,29–34] A total of 146 stroke subjects were included. Studies were heterogeneous regarding study population included and methods used (Table 1). Serious adverse events were not described. Figure 1 illustrates the electrode positions used in the studies.

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 hemispatial neglect with 2 mA anodal tDCS, compared to sham treatment.[31] The remaining studies showed a significant improvement with 1 or 2 mA anodal tDCS (compared to sham stimulation) but only for some of the performed tests.[20,30,33,34]

Facilitatory tDCS over the contralesional hemisphere

Only one study investigated the efficiency of 1 mA anodal tDCS over the contralesional hemisphere.[33] The results showed no treatment-related improvement of hemispatial neglect, compared to sham tDCS.

Inhibitory tDCS over the contralesional hemisphere

Three studies probed the effect of cathodal tDCS over the contalesional hemisphere in comparison to sham stimulation. Two of them revealed significant treatment-related positive effects of real 2 mA[34] and real 1 mA[33] tDCS, again only for a sub-group of hemispatial neglect tests performed. One study detected a deteriorating effect of real 2 mA tDCS.[31]

Bilateral tDCS

Four controlled studies tested the efficiency of bilateral tDCS. Two studies revealed a significant improvement of hemispatial neglect with 1 mA bilateral tDCS, compared to sham stimulation.[20,29] One study showed a significant improvement with 1.5–2 mA bilateral tDCS combined with optokinetic treatment in subacute stroke, but only in a sub-set of tests performed[22] One study found no treatment-related effect of 2 mA bilateral tDCS on improvement of chronic hemispatial neglect.[32]

Comparison of different protocols

Four trials compared different tDCS protocols to improve hemispatial 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.[31] Two found no significant treatment-related effects on hemispatial neglect.[33,34] One study compared anodal tDCS over the ipsilesional hemisphere with bilateral tDCS and found a significant greater improvement with bilateral tDCS.[20]

Summary

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

Repetitive transcranial magnetic stimulation

Twelve controlled studies investigated the effect of rTMS on recovery of hemispatial neglect.[35,19,36–45] These studies included a total of 297 stroke subjects. There is a large variability of methods and of subjects included among these trials (Table 2). No study describes serious adverse events.

TABLE 1. Overview of studies investigating tDCS for recovery of hemispatial neglect.

Reference	Number of participants/ gender	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.[22]	32/21 males, 11 females	25 ± 17 days	na/na/20 right hemisphere, 12 left hemisphere	Parallel groups (16+16)/no blinding	(1) 1.5–2 mA 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	1.5–2 mA bilateral tDCS combined with an optokinetic task significantly better than no intervention: spontaneous body orientation, Clock Drawing Test, line bisection, and Apples Cancellation Task – egocentric neglect No treatment significantly better than 1.5–2 mA bilateral tDCS combined with an optokinetic task: Apples Cancellation Task – allocentric neglect
Ko et al.[30]	15/10 males, 5 females	47 ± 18 days	10 ischemic, 5 hemorrhagic/9 cortical, 6 subcortical/right hemisphere	Crossover (15/15)/ double blinding	(1) 2 mA anodal tDCS (20 min) over P4 (2) Sham tDCS (20 min, current turned off after 10 s) over P4	1 session/evaluations: T1 before treatment, T2 immediately after treatment	2 mA anodal tDCS significantly better than sham tDCS: line bisection test and shape-unstructured cancellation test No significant differences: letter-structured cancellation test
Bang et al.[29]	12/4 males, 8 females	6.6 ± 1.7 weeks	na/na/right hemisphere	Parallel groups (6+6)/no blinding	(1) 1 mA 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	1 mA bilateral tDCS significantly better than no tDCS: motor-free visual perception and line bisection test
Sparing et al.[33]	10/ 4 males, 6 females	2.9 ± 3.5 months	na/na/right hemisphere	Crossover (10/10/10/ 10)/no blinding	(1) 1 mA anodal tDCS (10 min) over P3 (2) 1 mA cathodal tDCS (10 min) over P3 (3) 1 mA anodal tDCS (10 min) over P4 (4) Sham tDCS (10 min, current turned off after 30 s) over P4	1 session/evaluations: T1 before treatment, T2 after treatment	1 mA cathodal tDCS contralesional and 1 mA anodal tDCS ipsilesional significantly better than 1 mA anodal tDCS contralesional and sham tDCS: line bisection task No significant differences: number of cancelled stimuli
Làdavas et al.[31]	30/16 males, 14 females	3.0 ± 1.6 months	na/na/right hemisphere	Parallel groups (11+8+11)/ double blinding	(1) 2 mA anodal tDCS (20 min) over P6 in combination with prism adaptation treatment (2) 2 mA cathodal tDCS (20 min) over P5 in combination with prism adaptation treatment (3) Sham tDCS (20 min, current turned off after 20 s) over P5/P6 in combination with prism adaptation treatment	10 sessions/evaluations: T1 within the week before treatment, T2 within the week after treatment	2 mA anodal tDCS significantly better than 2 mA cathodal tDCS and sham tDCS: Behaviural Inattention Test sham tDCS significantly better than cathodal tDCS: Behavioral Inattention Test

TABLE 1. (*Continued*)

Reference	Number of participants/gender	Time since stroke	Stroke etiology/lesion location/affected hemisphere	Study design/blinding	Treatment	Number of tDCS sessions/evaluations	Results (group*time effect/performed tests)
Smit et al.[32]	5/3 males, 2 females	4.8 ± 4.4 years	2 ischemic, 3 hemorrhagic/5 cortical/right hemisphere	Crossover (5/5)/double blinding	(1) 2 mA 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: Behavioral Inattention Test
Sunwoo et al.[20]	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) 1 mA bilateral tDCS (20 min) over P3 and P4 (2) 1 mA 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	1 mA bilateral tDCS significantly better than 1 mA anodal tDCS and sham tDCS: line bisection test 1 mA anodal tDCS significantly better than sham tDCS: line bisection test No significant differences: star cancellation test
Yi et al.[34]	32/22 males, 10 females	na	26 ischemic, 4 hemorrhagic/27 cortical, 3 subcortical/right hemisphere	Parallel groups (10+10+10)/no blinding	(1) 2 mA anodal tDCS (30 min) over P4 in combination with occupational therapy (2) 2 mA cathodal tDCS (30 min) over P3 in combination with occupational therapy (3) Sham tDCS (30 min, current turned off after 30 s) over P4 in combination with occupational therapy	15 sessions/evaluations: T1 before treatment, T2 1 week after treatment	2 mA anodal tDCS and 2 mA cathodal tDCS significantly better than sham tDCS: motor-free visual perception test, star cancellation test, and line bisection test No significant differences: Catherine Bergego Scale

Notes: mA = milliampere; na = not available, not applicable; and tDCS = transcranial direct current stimulation.

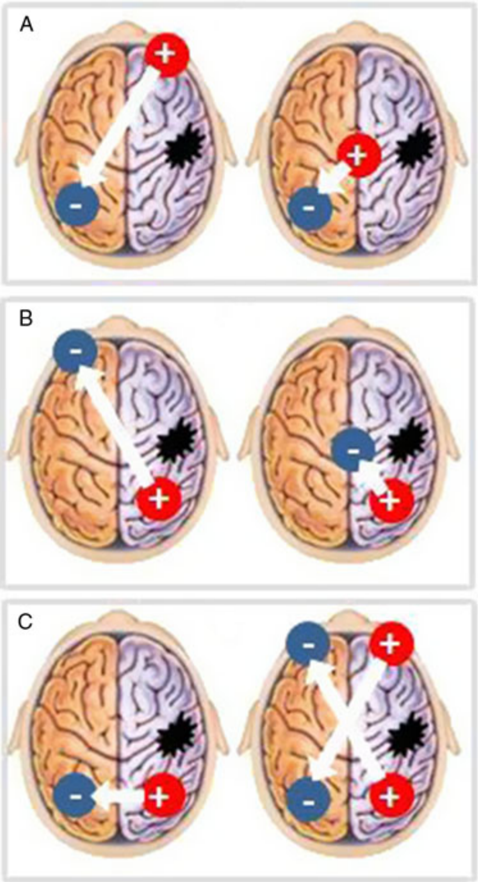

FIGURE 1. Positioning of the anode and of the cathode during (A) inhibitory tDCS over the contralesional hemisphere, (B) facilitatory tDCS over the ipsilesional hemisphere, and (C) bilateral stimulation. + = anode; − = cathode.

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 10 Hz rTMS (compared to sham), but one of them only in a sub-set of tests.[40]

Inhibitory rTMS over the contralesional hemisphere

Five controlled studies tested the effect of (cTBS) over the contralesional hemisphere on improvement of hemispatial neglect.[35,37,38,42,44] 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 1 Hz rTMS[37,39,40,41,43–45] and 0.5 Hz rTMS[19] over the contralesional hemisphere. Five of them found a significant greater improvement with real rTMS in each assessment performed.[19,37,39,43,44] Two studies found a greater improvement with rTMS in only a subset of tests performed.[40,45] One study showed no supportive effect of rTMS.[41]

Comparison of different protocols

Only two studies compared the efficiency of different rTMS protocols in the rehabilitation of hemispatial neglect. 10 Hz rTMS over the ipsilesional hemisphere was compared to 1 Hz rTMS[40] or cTBS[44] over the contralesional hemisphere. The results indicate the best improvement with cTBS and the smallest improvement with 1 Hz rTMS.

Summary

The major part of available data implies a positive influence of rTMS on recovery from hemispatial neglect after stroke. Based on current data, cTBS is the most effective stimulation technique. In contrast, conventional rTMS over the contralesional hemisphere appears to be less efficient (Figure 2). Future studies should compare facilitatory and inhibitory rTMS protocols within larger study cohorts and include long-term follow-up investigations.

Discussion

This review analyzed data from 20 controlled intervention trials including a total of 443 stroke patients with hemispatial neglect. Collectively the data suggest a positive effect of noninvasive brain stimulation to improve hemispatial 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.

Stimulation protocols

Inhibitory rTMS over the parietal lobe of the contralesional hemisphere is the most widely used stimulation protocol in rehabilitation of hemispatial neglect after stroke. Its efficiency was tested in 170 patients. Other rTMS protocols were less frequently applied (between 13 and 48 patients). In 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 hemispatial neglect after stroke has been used only when applying 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.[22,46,47,48]

Study or subgroup	Stimulation technique	Stimulation protocol, stimulated hemisphere	Effect size	Lower limit	Upper limit
Làdavas et al., 2015	tDCS	2 mA cathodal CL	-0.53	-1.42	0.37
Lim et al., 2010	rTMS	1 Hz CL	-0.11	-1.18	0.96
Sunwoo et al., 2014	tDCS	1 mA anodal IL	0.27	-0.61	1.15
Sunwoo et al., 2014	tDCS	1 mA cathodal+anodal IL+CL	0.31	-0.57	1.19
Sparing et al., 2009	tDCS	1 mA anodal CL	0.33	-0.58	1.25
Yang et al., 2016	rTMS	1 Hz CL	0.45	-0.18	1.08
Yi et al., 2016	tDCS	2 mA cathodal CL	0.54	-0.35	1.44
Yi et al., 2016	tDCS	2 mA anodal IL	0.59	-0.30	1.49
Turgut at al., 2016	tDCS	1.5–2mA cathodal+anodal CL+IL	0.76	0.04	1.48
Ko et al., 2008	tDCS	2 mA anodal IL	0.93	0.18	1.68
Làdavas et al., 2015	tDCS	2 mA anodal IL	1.05	0.16	1.94
Sparing et al., 2009	tDCS	1 mA anodal IL	1.08	0.12	2.05
Koch et al., 2012	rTMS	cTBS CL	1.09	0.10	2.08
Song et al., 2009	rTMS	0.5Hz CL	1.33	0.17	2.48
Kim et al., 2013	rTMS	1 Hz CL	1.86	0.74	2.98
Kim et al., 2013	rTMS	10 Hz IL	1.87	0.74	3.01
Sparing et al., 2009	tDCS	1 mA cathodal CL	1.90	0.81	2.98
Cha et al., 2015	rTMS	1 Hz CL	2.21	1.30	3.12
Olivieri et al., 2001	rTMS	25 Hz CL	2.33	0.97	3.68
Bang et al., 2015	tDCS	1 mA cathodal+anodal CL+IL	2.34	0.84	3.83
Fu et al., 2015	rTMS	cTBS CL	2.49	1.20	3.77
Nyffeler et al., 2009	rTMS	cTBS CL	2.36	0.73	3.98
Yang et al., 2015	rTMS	1 Hz CL	3.01	1.68	4.33
Yang et al., 2015	rTMS	10 Hz IL	3.06	1.76	4.37
Cazzoli et al., 2012	rTMS	cTBS CL	3.53	1.93	5.13
Yang et al., 2015	rTMS	cTBS CL	3.76	2.24	5.28
Kim et al., 2015	rTMS	1 Hz CL	5.17	3.74	6.61
Subtotal	tDCS	CL+IL	0.96	0.44	1.47
Subtotal	tDCS	IL	0.83	0.44	1.21
Subtotal	tDCS	CL	0.59	0.13	1.03
Subtotal	**tDCS**		0.79	0.53	1.04
Subtotal	cTBS	CL	2.79	2.16	3.37
Subtotal	rTMS	IL	2.62	1.70	3.42
Subtotal	rTMS	CL	2.26	1.88	2.63
Subtotal	**rTMS**		2.45	2.15	2.74
Total			1.69	1.49	1.88

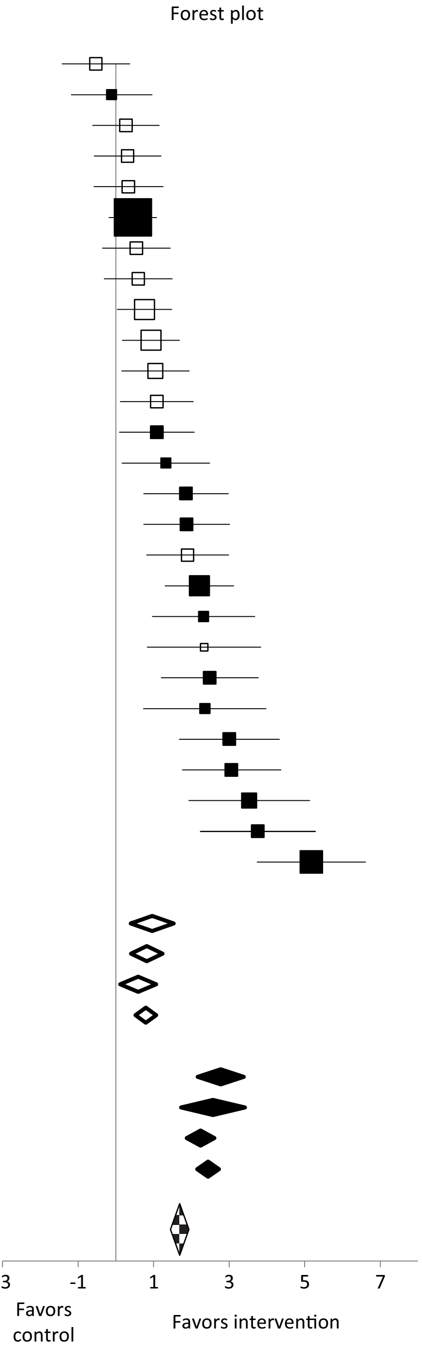

FIGURE 2. Overview of effect size and 95% confidence interval for neglect outcome measures. CL = contralesional; cTBS = continuous theta burst stimulation; Hz = Hertz; IL = ipsilesional; mA = milliampere; rTMS = repetitive transcranial magnetic stimulation; tDCS = transcranial direct current stimulation; ■,◆ = repetitive transcranial magnetic stimulation; and □,◊ = transcranial direct current stimulation.

Current data indicate (1) stimulation-method-dependent efficiency and (2) stimulation-protocol-dependent efficiency to improve hemispatial neglect after stroke. Figure 1 illustrates that rTMS appears to be more effective than tDCS in improving hemispatial neglect after stroke. In addition, inhibitory stimulation of the contralesional hemisphere appears to be the less effective stimulation protocol. In contrast, bilateral tDCS and cTBS show the best efficiency. However, more data are needed to allow definite conclusions about the efficiency of diverse tDCS/rTMS protocols.

TABLE 2. Overview of studies investigating rTMS for recovery of hemispatial neglect.

Reference	Number of participants, gender, 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.[40]	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) 1 Hz rTMS (1200 pulses 90% rMT, coil sagittally, handle posterior) over P3 (2) 10 Hz 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	1 Hz and 10 Hz rTMS significantly better than sham rTMS: Korean-Modified Barthel Index 10 Hz rTMS significantly better than sham rTMS: line bisection test No significant differences: Motor-Fee Visual Perception Test, star cancellation test, and Catherine Bergego Scale
Olivieri et al.[43]	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) 25 Hz 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	25 Hz rTMS significantly better than sham rTMS: line bisection test
Cazzoli et al.[36]	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	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, and two part picture test
					(2) Sham rTMS (sham coil) over P3, then cTBS (801 pulses 100% rMT, coil tangentially, handle posteriorly) over P3		cTBS significantly better than sham rTMS: Catherine Bergego Scale, Vienna Test System, random shape cancellation test, and two part picture test
					(3) No rTMS		No significant differences: Munich reding texts
Song et al.[19]	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 EEGSystem	(1) 0.5 Hz 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	0.5 Hz rTMS significantly better than no rTMS: line bisection test, and star cancellation test
Yang et al.[45]	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) 1 Hz rTMS (900 pulses 90% rMT, coil tangentially) over P5 in combination with sensory cueing (2) 1 Hz 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	1 Hz rTMS combined with sensory cueing and 1 Hz rTMS significantly better than no treatment: Behavioral Inattention Test No significant differences: Catherine Bergego Scale

TABLE 2. (*Continued*)

Reference	Number of participants, gender, 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.[38]	20/16 males, 4 females	19-114 days	9 ischemic, 11hemorrhagic, 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, and star cancellation test
Koch et al.[35]	18/na	subacut	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, corresponding to P4 (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.[44]	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) 1 Hz rTMS (656 pulses 80% rMT) over P3 (2) 10 Hz 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	1 Hz cTBS significantly better than 1 Hz, 10 Hz, and sham rTMS: star cancellation test 1 Hz and 10 Hz rTMS significantly better than sham rTMS: star cancellation test 1 Hz rTMS and cTBS significantly better than 10Hz and sham rTMS: line bisection test 10 Hz rTMS significantly better than sham rTMS: line bisection test
Lim et al.[41]	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) 1 Hz 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, and line bisection test

TABLE 2. (*Continued*)

Reference	Number of participants, gender, 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)
Cha et al.[37]	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) 1 Hz 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	1 Hz rTMS significantly better than sham rTMS: line bisection test, and Albert Test
Nyffeler et al.[42]	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 h after treatment, T3 8 h after treatment	cTBS significantly better than sham rTMS and no rTMS: perceived left visual targets, and reaction time left
Kim et al.[39]	34/15 males, 19 females	19 ± 12 months	ischemic, hemorrhagic/ 18 cortical, 14 subcortical/right hemisphere	Parallel groups (15+19)/no blinding/10–20 System	(1) 1 Hz rTMS (1200 pulses 90% rMT) over P3 (10 sessions) (2) 1 Hz rTMS (1200 pulses 90% rMT) over P3 (1 session)	10 sessions, 1 session/evaluations: T1 before treatment, T2 after treatment	10 sessions of 1 Hz rTMS significantly better than 1 session of 1 Hz rTMS: letter cancellation test, line bisection test, and Ota's task

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

Study design

Current studies investigating rTMS and tDCS to improve hemispatial neglect after stroke 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: eight sessions on average per study and rTMS: 16 sessions on average per study), and (3) long-term follow-up investigation (tDCS: only one study with follow-up over 5 days and rTMS: seven studies with follow-up up to 6 weeks). In consequence, more data are needed to evaluate the long-term effectiveness of the repetitive application of noninvasive brain stimulation for improving hemispatial neglect after stroke.

Only a small part of current studies (four studies evaluating tDCS and four studies evaluating rTMS) mentioned a double-blinded study design. However, blinding of both patients and investigators is critical for the interpretation of meta-analyses. In future, more double-blinded studies are needed to exclude confounders and allow reliable evaluation of the effects of noninvasive brain stimulation on recovery from hemispatial neglect after stroke. Another limitation of the pertinent literature is a lack of elaborate neuro-navigation techniques to position and maintain accurate coil positioning during the rTMS intervention. The majority of studies used coil positioning based on the international 10–20 system.

Patient characteristics

At present, noninvasive brain stimulation techniques have mostly been applied in subacute and chronic stroke survivors with hemispatial 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 with 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 hemispatial neglect may differ in ischemic and hemorrhagic stroke, as it may do in different lesion locations and distributions within the brain.

Limitations

The studies included in our review show a large variability of study population (time from stroke, stroke etiology, and stroke location), stimulation protocols used (tDCS/rTMS intensity, duration, number of sessions, stimulated hemisphere, and stimulated area), assessment methods, study design (parallel groups/crossover, and with/without an additional intervention), and methodological quality (blinding, and sham condition technique). All these in-between-study inconsistencies taint the comparison of effect sizes.

Disclosures

Jitka Veldema, Kathrin Bösl, Günter Neumann, Geert Verheyden, and Dennis Alexander Nowak have nothing to disclose.

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