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Update article

Hemi-spatial neglect rehabilitation using non-invasive brain stimulation: Or how to modulate the disconnection syndrome?

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ABSTRACT

Hemi-spatial neglect syndrome is common and sometimes long-lasting. It is characterized by a deficit in the use and awareness of one side of space, most often consecutive to a right hemisphere injury, mainly in the parietal region. Acknowledging the different types and all clinical characteristics is essential for an appropriate evaluation and adapted rehabilitation care management, especially as it constitutes a predictive factor of a poor functional prognosis. Some new approaches have been developed in the last fifteen years in the field of hemi-spatial neglect rehabilitation, where non-invasive brain stimulation (TMS and tDCS) holds an important place. Today's approaches of unilateral spatial neglect modulation via non-invasive brain stimulation are essentially based on the concept of inter-hemispheric inhibition, suggesting an over-activation of the contralesional hemisphere due to a decrease of the inhibiting influences of the injured hemisphere. Several approaches may then be used: stimulation of the injured right hemisphere, inhibition of the hyperactive left hemisphere, or a combination of both. Results are promising, but the following complementary aspects must be refined before a more systematic application: optimal stimulation protocol, individual management according to the injured region, intensity, duration and frequency of care management, delay post-stroke before the beginning of treatment, combination of different approaches, as well as prognostic and efficacy criteria. An encouraging perspective for the future is the combination of several types of approaches, which would be largely facilitated by the improvement of fundamental knowledge on neglect mechanisms, which could in the future refine the choice for the most appropriate treatment(s) for a given patient.

1. Introduction

Hemi-spatial neglect syndrome has a particular place among pathologies affecting the integration of spatial information. It constitutes a spatial cognition disorder frequently observed after stroke. This disorder characterized by a deficit in the use of and awareness of one side of space is a long-lasting phenomenon, most often occurring after a right hemispheric injury, noticeably in the parietal region [1] and specifically around the inferior parietal lobule, i.e. around a region playing the role of a multi-sensory and sensorimotor interface between spatial perception and action.

This multi-faceted syndrome associates a deficit in taking into account sensory information stemming from the part located on the contralateral side of the brain injury, a change in orientation with reactions and actions directed towards that side, as well as behavioral symptoms resulting from the altered awareness of the patient regarding these disruptions.

Taking into account this diversity and all the clinical characteristics is essential for a more appropriate evaluation and adapted care management rehabilitation. This is even more relevant since spatial cognition disorders, and above all hemi-spatial neglect, are at the source of major limitations of activities and constitute a predictive factor of a poor functional prognosis, delaying the recovery of cognitive and motor autonomy [2–7]. Taking into account this syndrome is thus a real therapeutic challenge in the rehabilitation care management of these patients, to try and reduce the disability and improve the prognosis.

Two main theoretical tendencies can be differentiated in unilateral neglect rehabilitation: top-down and bottom-up approaches (see reviews in [8–10]). More recently, transversal approaches have been developed, targeting more specifically

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impairments with no spatial laterality frequently associated to spatial neglect.

Among the therapeutic axes recently developed, some of them appear particularly promising (see review in [11]). The use of non-invasive brain stimulation in patients has been widely reported for its high therapeutic relevance (see [12,13]), especially in the framework of research on spatial neglect: Transcranial Magnetic Stimulation (TMS) and transcranial Direct Current Stimulation (tDCS) are used to improve symptoms of patients with visuo-spatial disorders.

Non-invasive brain stimulation using Transcranial Magnetic Stimulation (TMS) and transcranial Direct Current Stimulation (tDCS) can be used not only as a diagnostic research tool to explore pathophysiological aspects of spatial neglect, but also to improve symptoms.

The objective of this literature review is to provide an overview of the various paradigms used in this context, for exploratory and/or therapeutic uses, in the framework of single-case studies or randomized, controlled trials.

This literature review focused on publications in the English language indexed in PubMed pertaining to the use of one of these techniques for evaluation purposes or to improve symptoms in patients presenting post-stroke hemi-spatial neglect. For the search, the following keywords were combined: "TMS or tDCS or transcranial magnetic stimulation or transcranial direct current stimulation" and "spatial neglect or visual neglect or hemi-spatial neglect or visuo-spatial neglect". By reading the titles and abstracts, original articles or reviews of the existing literature were selected. References of selected articles were also studied in order to find additional ones. Table 1 lists the different studies selected pertaining to the clinical use of one or the other techniques, according to the type of symptoms improved (deficits) and/or the functional impact in terms of activity limitations.

Table 1
Nature of improvements according to the International Classification of Functioning.

Deficits	
Visuomotor tasks (line bisection, line crossing, drawing tests)	Oliveri et al., 2001
	Brighina et al., 2003[a]
	Shindo et al., 2006[a]
	Song et al., 2009[a]
	Lim et al., 2010[a]
	Koch et al., 2012[a]
	Cazzoli et al., 2012[a]
	Kim et al., 2013[a]
	Kim et al., 2014[a]
	Ko et al., 2008
	Sparing et al., 2009
	Sunwoo et al., 2013
	Brem et al., 2014[a]
Visual and verbal tasks (object description, image description)	Koch et al., 2008
	Cazzoli et al., 2012[a]
Tactile extinction	Oliveri et al., 1999
Visual extinction	Nyffeler et al., 2009
Visual perception	Cazzoli et al., 2012[a]
	Kim et al., 2013[a]
	Sparing et al., 2009
Activity limitations	
Barthel index	Shindo et al., 2006[a]
	Kim et al., 2013[a]
Behavioral BIT	Koch et al., 2012[a]
Reading	Cazzoli et al., 2012[a]
Activities of daily living	Shindo et al., 2006[a]
	Cazzoli et al., 2012[a]
	Kim et al., 2013[a]
	Brem et al., 2014[a]
Participation limitations (disability)	
	No studies

In bold: tDCS studies.
[a] Indicates repeated sessions.

2. Facilitating or inhibiting effects of non-invasive brain stimulation

According to the protocol used, brain stimulation can have opposite effects on the underlying brain tissues: low-frequency rTMS (1 Hz), continuous Theta Burst Stimulation (TBS) and cathodal tDCS decrease cortical excitability, whereas high-frequency rTMS (5 Hz) intermittent Theta Burst Stimulation and anodal tDCS seem to increase cortical excitability with facilitating effects [14–21].

3. Rationale of use in the context of spatial neglect

To understand the different types of modulation of visuo-spatial functions via non-invasive brain stimulation, it seems relevant to briefly review the attention networks involved in visuo-spatial neglect and clarify the concept of inter-hemispheric competition. Visuo-spatial neglect is more and more defined as resulting from the interruption of the fronto-parietal attention networks, especially those located in the right hemisphere [22–25]. Furthermore, as suggested by Kinsbourne [26,27], both parietal cortices, right and left, exert between themselves a reciprocal inter-hemispheric inhibition. Thus, after a parietal injury to the right hemisphere, we observe not only a decreased activity in this injured region, but also a disinhibition of the contralateral left hemispheric region. This inter-hemispheric of the left hemisphere worsens the tendency of patients with spatial neglect to only pay attention to the right side and disregard the left side. This has been underlined by clinical observations and functional imaging data. Vuilleumier et al. [28] reported a unique case of one patient with two successive sequential lesions the first on the right hemisphere followed by a second on the left hemisphere, the first lesion led to severe left spatial neglect, which resolved itself after the onset of the second lesion. The longitudinal follow-up via fMRI of patients with spatial neglect [29] highlighted an initial over-activation on the healthy side. The clinical recovery of spatial neglect was associated with an increased activation of certain right hemispheric regions, but also activation changes on the healthy left side, leading to a reduction of the inter-hemispheric imbalance. The recovery of spatial neglect-related attention deficits thus seems correlated to a reactivation and a recalibration of functional and structural activity within the fronto-parietal networks involved.

Today's approaches on neglect modulation are thus essentially based on this neurophysiological concept of inter-hemispheric inhibition, suggesting an over-activation of the contralesional hemisphere due to the decreased inhibiting influences of the injured hemisphere.

Based on this notion, 3 approaches seem valid (Fig. 1): stimulation of the injured right hemisphere, inhibition of the hyperactive left hemisphere or a combination of both. To date, most studies on non-invasive brain stimulation targeting neglect have chosen to inhibit the left hemisphere, but the facilitating protocols to increase the functions of ipsilesional neural circuits merit further development. One of the potential barriers to this latter approach, especially with TMS, could be the increased risk of seizure.

The main studies are listed in Table 1.

Table 2 (TMS) and Table 3 (tDCS) review the different studies retained for this review, with a brief description of the type of study, stimulation parameters used, evaluation tests as well as main results reported.

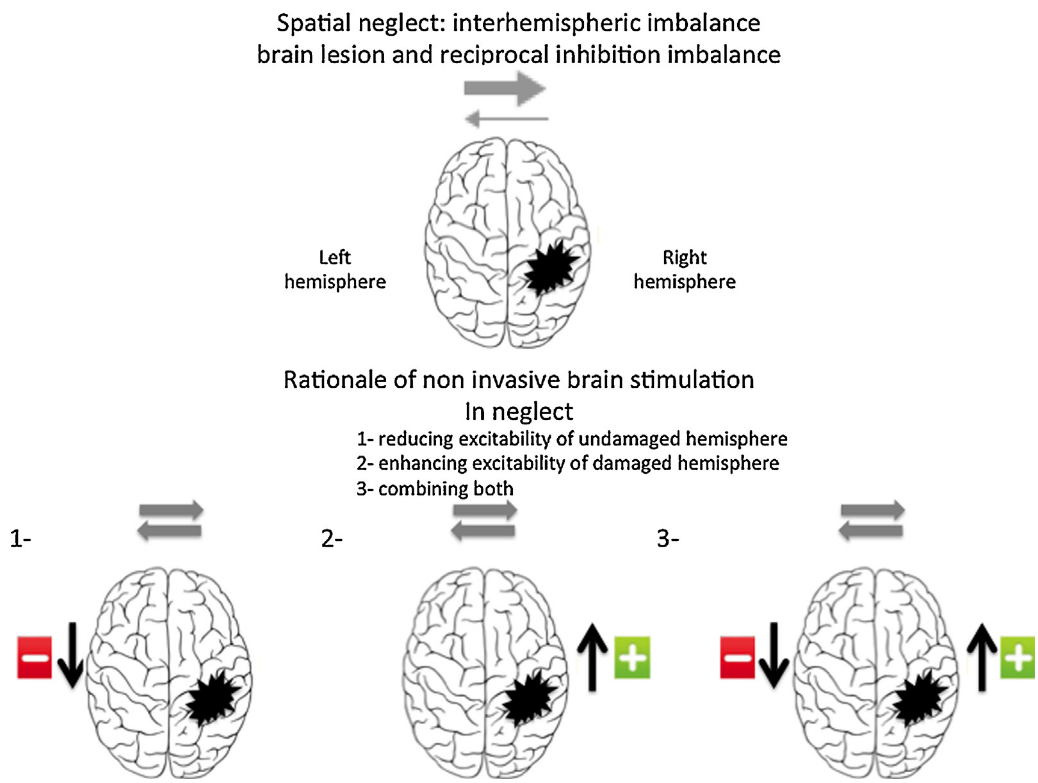

Fig. 1. Spatial neglect: inter-hemispheric imbalance brain lesion and reciprocal inhibition imbalance.

4. TMS and spatial neglect

Oliveri et al. [30,31] were the first to evaluate the effects of TMS, first on-line (i.e. during stimulation). The first study measured the level of tactile extinction in 2 groups of patients with right and left hemispheric injuries, by applying TMS at parietal or frontal level on the contralesional side. Only the application of TMS on the frontal region on the left hemisphere in patients with an injured right hemisphere allowed the decrease of the contralateral extinction, suggesting a specificity for the injured side and the stimulated site. Later on, the application of inhibiting rTMS above the healthy parietal cortex in patients with right and left hemi-spatial neglect, during a task of assessing the length of several lines (Landmark-type) led to a transient decrease of the neglect, the effects were only observed during the duration of the stimulation.

Later studies evaluated the effects of off-line stimulation (i.e. after the stimulation period) according to protocols with a single stimulation session [32–34] or repeated stimulation sessions [34–41].

Brighina et al. [35] used low-frequency rTMS (1 Hz), applied over the left parietal cortex in 3 patients with spatial neglect and lesion of the right hemisphere, less than 6 months post-stroke. Seven sessions spread over a 14-day period were performed. The evaluation included the landmark task, a line bisection task and clock drawing, and was performed 15 days before treatment, the first and last day of treatment as well as 15 days post-treatment. The first two evaluations (pre-treatment) showed an important bias towards the right side for all tests used, with a significant decrease of this bias at the end of the stimulation protocol, and lasting 15 days post-treatment.

Shindo et al. [36] also evaluated the effect of inhibiting rTMS on the healthy parietal cortex in 2 patients with chronic spatial neglect ($>$ 6 months). Patients had 6 sessions over a 2-week period. The clinical evaluation included neglect tests from the Behavioral Inattention Test (BIT), MMSE, motor recovery index and the Barthel index. This clinical assessment was performed 6 times (twice before treatment, at Day 1, at the end of treatment and at 4 and 6 weeks post-treatment). Results showed an improvement on the BIT and bisection tests, lingering at 6 weeks post-treatment, but no improvements were reported on the other parameters.

After one single session of low-frequency rTMS, Koch et al. [32] highlighted a decrease in neglect symptoms (denomination of chimeric visual objects) in 10 patients with right hemispheric damage. This clinical improvement was associated with a decrease in the pathological left PPC-M1 (posterior parietal cortex and primary motor cortex) evidenced in these patients, reinforcing the notion of inter-hemispheric rebalancing via inhibiting stimulation on the healthy side.

In the study by Song et al. [37], two daily rTMS sessions (above the left PPC) were done for 14 days in 14 patients with hemi-spatial neglect (7 rTMS and 7 controls), less than 2 months post-stroke. The evaluation used the line bisection and line crossing tests 2 weeks before treatment, then at the beginning and end of the treatment and finally 2 weeks post-treatment. Results showed an improvement of performances in both tasks for the treated group vs controls with sustainable results 14 days post-treatment.

Using the new continuous inhibiting Theta burst stimulation protocol above the left PPC, Nyffeler et al. [33] evaluated in 11 neglect patients the variation of consecutive effects according to the application of 2 or 4 TBS trains vs placebo stimulation and monitored the sustainability of these affects after this unique session up to 8 hours (2 TBS trains) or 96 hours (4 TBS trains). They reported an increased detection rate for the visual targets in the left hemi-space, associated with a decreased reaction time, up to 8 hours for the 2 $\times$ TBS and 32 h for the 4 $\times$ TBS.

Lim et al. [38] also proposed a protocol of repeated inhibiting rTMS sessions on the healthy side, for a total of 10 sessions (5 per week over a 2-week period), and performing rTMS just before occupational therapy training. Fourteen patients were evaluated twice (7 rTMS and occupational therapy, 7 occupational therapy alone) with the Schenkenberg's line bisection test and the Albert's line crossing test (D-1 pre-treatment and D + 1 post-treatment) the

Table 2
Use of Transcranial Magnetic Stimulation (TMS) in post brain damage neglect.

Authors, year	Type of study	Stimulation parameters	Positioning method	Patients	Delay	Evaluations	Significant results
Oliveri et al., 1999 [30]	Controlled study (stimulation site)	Single pulse TMS F3 F4 and P3 P4, unaffected hemisphere	10/20 EEG system	14 RBD 14 LBD	1–4 m	Contralateral extinction	Extinction reduction only for RBD patients and F stimulation
Oliveri et al., 2001 [31]	Controlled study (rTMS vs sham)	rTMS P5 P6 unaffected hemisphere	10/20 EEG system	5 RBD 2 LBD	1–48 w	Task length judgment	Reduced ipsilesional attentional bias RBD and LBD patients
Brighina et al., 2003[a] [35]	Uncontrolled pilot study	1 Hz rTMS P5 unaffected hemisphere 7 sessions, 2 w	10/20 EEG system	3 RBD N+	3–5 m	Landmark Clock drawing Line bisection	Improvement in the 3 tasks, maintained 15 days after
Shindo et al., 2006[a] [36]	Uncontrolled pilot study	0.9 Hz rTMS P5 unaffected hemisphere 6 sessions, 2 w	10/20 EEG system	2 RBD N+	6 m	BIT MMSE or HDS-R BRS Barthel Index	BIT improvement, maintained at 6 weeks
Koch et al., 2008 [32]	Experiment 1 Controlled study	ppTMS conditioning left PPC (P3) – test M1	10/20 EEG system	12 RBD N+ 8 RBD N– 10 healthy controls	91.6d 83.9d	left PPC-M1 effects: MEPs amplitude	Pathologically increased left PPC-M1 effects observed selectively in the N+ group, correlated with severity of neglect
Koch et al., 2008 [32]	Experiment 2 Controlled study	1 Hz rTMS left PPC (P3)	10/20 EEG system	10 RBD N+ 5 RBD N–		MEPs amplitude Visual chimeric objects naming	Normalization of the abnormal left PPC-M1 influences in N+ Improvement of the experimental visual chimeric test
Song et al., 2009[a] [37]	Randomized study, controlled vs sham	0.5 Hz rTMS left PPC (P3) 2 groups:	10/20 EEG system	14 RBD N+	21–60d	Line bisection Line cancellation	Improvement in both tasks, stable by 2 weeks
		rTMS sham 20 sessions (2/d, 2 w)		7 7			
Nyffeler et al., 2009 [33]	Randomized controlled study	cTBS left PPC (P3)	10/20 EEG system	11 RBD N+	0.4–36.1 m	Visual perception task (PVT)	Improvement of targets' perception on the left side Decreased RT for left-sided targets
		4 conditions: no intervention 2 sham trains 2 TBS trains 4 TBS trains		5 patients/exp			
Lim et al., 2010[a] [38]	Comparative open pilot study	1 Hz rTMS left PPC (P5) 2 groups:	10/20 EEG system	14 RBD N+		Schenkenberg test Albert test	Improvement in line bisection
		rTMS + BT rTMS immediately prior to BT		7	61.9d		
		BT 30 mn top-down approach		7	139.0d		
Koch et al., 2012[a] [39]	Randomized study, controlled vs sham, double-blind	cTBS left PPC (P3) 10 sessions (1/d, 2 w)	Neuronavigation system	18 RBD N+	25–100d	left PPC-M1 connectivity (MEPs amplitude) BIT (C + B)	Reduction of hyper-excitability of LH parieto-frontal circuits Improvement of neglect symptoms (BIT)
Cazzoli et al., 2012[a] [40]	Randomized study, controlled vs sham, double-blind	cTBS left PPC (P3)	10/20 EEG system	24 RBD N+	26.63d	Visual perception task (PVT)	Improvement of detection of left-sided visual targets

Table 2 (*Continued*)

Authors, year	Type of study	Stimulation parameters	Positioning method	Patients	Delay	Evaluations	Significant results
		3 groups:					
		cTBS-sham		8		Shape cancellation test	Improvement in the paper-pencil assessment
		sham-cTBS		8		Picture scanning test	Improvement in the activities of daily living
		no stim		8		Texts reading CBS	
Kim et al., 2013[a] [41]	Randomized study, controlled vs sham, double-blind	rTMS	10/20 EEG system	27 RBD N+	14.2–16.4d	MVPT	Improvement in line bisection (high frequency vs sham) Improvement of K-MBI score in the 2 rTMS groups
		3 groups					
		1 Hz left PPC (P3)		9		Line bisection	
		10 Hz right PPC (P4)		9		Star cancellation	
		sham		9		CBS	
		10 sessions (1/d, 2 w)				K-MBI	
Kim et al., 2015[a] [34]	Randomized controlled study	rTMS 1 Hz	10/20 EEG system	34 RBD N+	3–45 m	Line bisection Letter cancellation Ota's task	Improvement in all tasks with 10 sessions vs single session
		Left PPC (P3)					
		2 groups:					
		1 session		19			
		10 sessions (1/d, 2 w)		15			

rTMS: repetitive TMS; pp TMS: paired pulse TMS; RBD: right brain damaged; LBD: left brain damaged; N+: neglect; N−: no neglect; PPC: posterior parietal cortex; d, w, m: days, weeks, months; BIT: behavioral inattention test; HDS-R: revised Hasegawa dementia scale; MMSE: mini-mental state examination; BRS: Brunnstrom recovery stage; BI: Barthel index; K-MBI: Korean-modified Barthel index; MVPT: motor-free visual perception test; CBS: Catherine Bergego scale.
[a] Indicates repeated sessions.

results showed an absence of improvements for the line crossing test and an improvement on the line bisection test but only for the lines located on the left side.

More recently, Koch et al. [39] evaluated the effectiveness of continuous TBS with repeated sessions (10 sessions spread-out over a 2-week period), applied above the left PPC, in 18 patients with hemi-spatial neglect (9 cTBS and 9 placebo stimulation). The evaluation included the BIT (conventional and behavioral) as well as the study of PPC-M1 connectivity on the healthy side before treatment and up to 2 weeks later. BIT scores had improved up to 16.3% in the treated group right after treatment and up to 22.6% at 1 month after the beginning of the treatment. In parallel, authors noted, only in the treated group, a decreased of the abnormal over-excitability for the functional connections of the left PPC.

In a controlled, double-blind study, Cazzoli et al. [40] applied 4 cTBS trains above the left PPC in 2 sessions performed over 2 consecutive days. In all, 24 neglect patients were evaluated, at the sub-acute post-stroke phase (mean delay post-stroke: 27 days), 8 patients benefited from the real stimulation followed by placebo, 8 patients had placebo stimulation followed by real stimulation, and 8 patients had no stimulation. Evaluations included a visual perception task, a line crossing test, an image description test, a reading test and the Catherine Bergego scale. These evaluations were performed one week before, then 1, 2 and 3 weeks later. Results showed 37% improvement in the spontaneous behavior of patients in activities of daily living (ADL) after continuous TBS, lingering up to 3 weeks post stimulation. This improvement was also associated with better performances on the neuropsychological tests.

Kim et al. [41] also assessed patients with hemi-spatial neglect ($n = 27$) at an early phase (14 to 16 days post-stroke), in a randomized, controlled study, comparing the effects of low-frequency inhibitory stimulation above the left PPC vs high-frequency excitatory stimulation above the right PPC vs placebo stimulation. In all, 10 sessions were performed over a 2-week period, with an evaluation before and right after the 10 sessions (visual perception test, line bisection test, star cancellation test, Catherine Bergego scale and Barthel index). Results showed an improvement of the Barthel index for the two treated groups with an improvement in the line bisection test only for the high-frequency group. This is the first study demonstrating a potential benefit of high-frequency rTMS on neglect, at a sub-acute stage, without adverse events.

Finally, Kim et al. [34] compared the effect of one single session vs 10 sessions of inhibiting rTMS in 34 patients with chronic hemi-spatial neglect. The evaluation performed before and after the treatment included a line bisection test a letter cancellation test, and the Ota gap-detection test. Results showed an improvement in both conditions (single session vs 10 sessions) for the line bisection and letter cancellation tests, this improvement was significantly higher for the group with repeated sessions. Regarding the Ota gap-detection test, the combined improvement of the two components of hemi-spatial neglect (egocentric and allocentric neglect) was only found for the group that benefited from repeated sessions.

5. tDCS and spatial neglect

Only rare studies were conducted using tDCS in the context of spatial neglect. Maybe due to the better tolerance, especially in terms of risk of seizures, some of these studies were able to evaluate the benefit of ipsilesional stimulations.

Table 3
Use of transcranial Direct Current Stimulation (tDCS) in post brain damage neglect.

Authors, year	Type of study	Stimulation parameters	Positioning method	Patients	Delay	Evaluations	Significant results
Ko et al., 2008 [42]	double-blind, crossover, sham-controlled study	a tDCS right PPC (P4) 2 mA, 20 mn real vs sham 48 h interval between two sessions	10/20 EEG system	15 RBD N+	29–99d	Line bisection Shape cancellation Letter cancellation	Improvement in line bisection and shape cancellation
Sparing et al., 2009 [43]	double-blind, crossover, sham-controlled study	4 conditions: a tDCS, left PPC (P3) c tDCS, left PPC (P3) a tDCS, right PPC (P4) sham tDCS, right PPC (P4) 2 mA, 20 mn	10/20 EEG system	10 RBD N+	15d–12 m	TAP sub-test 'neglect' Line bisection	No significant changes in TAP a tDCS P4 and c tDCS P3: improvement in line bisection
Sunwoo et al. 2013 [45]	double-blind, crossover, sham-controlled study	3 conditions: dual mode a tDCS P4 + c tDCS P3 single mode a tDCS P4 sham 1 mA, 20 mn	10/20 EEG system	10 RBD N+	1.1–196.1 m	Line bisection Star cancellation	Improvement after both dual and single mode in line bisection Dual mode stronger effect vs single mode
Brem et al. 2014[a] [46]	double-blind, sham-controlled single-case study	4 w of daily sessions (5 d/w, 30 mn) w1 w4: conventional therapy w2: d1 conventional + sham tDCS d5 conventional + biparietal tDCS (aP4 cP3) w3: d1 to d5: conventional + biparietal tDCS (aP4 + cP3) 1 mA, 20 mn	10/20 EEG system	1 RBD N+	26d	TAP sub-tests: covert attention, alertness (intrinsic and phasic), and visual field Star cancellation Line bisection Figure copying	Larger improvement after combined biparietal tDCS and cognitive training

a tDCS: anodal tDCS; c tDCS: cathodal tDCS; RBD: right brain damaged; N+: neglect; PPC: posterior parietal cortex; d, w, m: days, weeks, months; TAP: test for attentional performance; conventional neglect therapy: computerized training batteries (OK-neglect) (smooth pursuit eye movements (SPEM) and saccades training).
[a] Indicates repeated sessions.

In fact, Ko et al. [42] evaluated 15 patients with hemi-spatial neglect at a sub-acute stage, in a crossover, double-blind, controlled vs placebo clinical trial. All patients were stimulated with anodal tDCS (excitatory) and placebo stimulation according to a randomized order, with a 48-hour interval between two tDCS sessions. Anodal tDCS applied above the right PPC showed a significant improvement on the form cancellation test and the line bisection test, right after stimulation.

Sparing et al. [43] tested in a more exhaustive manner the hypothesis of inter-hemispheric competition. A total of 10 patients with hemi-spatial neglect (post-stroke delay varied from 15 days to 1 year) were treated with tDCS under the following conditions:

- anodal tDCS (excitatory) above the undamaged left PPC;
- cathodal tDCS (inhibitory) above the same area;
- anodal tDCS above the right PPC;
- and placebo tDCS above the same region.

The different sessions were performed over two different days with a minimum inter-session interval of 3 hours, the order of the different conditions was counterbalanced according to the different subjects. The evaluation included a line bisection task and the "neglect" sub-test from the Tests of Attentional Performance (TAP) battery [44], performed before and after each stimulation condition. The results showed that both conditions – inhibitory effect of cathodal tDCS applied over the left hemisphere and facilitating effect of anodal tDCS applied above the right hemisphere – reduced the symptoms of hemi-spatial neglect for the line bisection test but not for the computer task of the TAP battery.

Following this reasoning, Sunwoo et al. [45] tested the effect of a combined application of excitatory anodal tDCS on the damaged side and inhibitory cathodal tDCS on the healthy side. Ten patients with hemi-spatial neglect at a chronic stage were evaluated, according to a crossover methodology, the order of the different stimulations (dual anodal and cathodal modality, anodal-only modality or placebo) were counterbalanced according to the subjects. The evaluation performed before and after each stimulation focused on a line bisection test and a star cancellation test. Results showed a reduction of the bias in the line bisection test for both real stimulation modalities, with a significantly more important effect for the dual stimulation modality. tDCS might be envisioned as a possible adjuvant treatment in the context of hemi-spatial neglect. However, effects on the medium and long term of this dual stimulation still need to be further investigated.

Finally, the idea of associating conventional rehabilitation during the stimulation phase was tested by Brem et al. [46] in a case study of one subject at the sub-acute phase. The patient benefited from 4 weeks of treatment, 5 days per week. The first and fourth weeks consisted of conventional rehabilitation care (optokinetic stimulation as well as smooth pursuit eye movements [SPEM] and saccades training). The second week associated conventional rehabilitation care and placebo tDCS on the first day, conventional rehabilitation care and tDCS on both PPC (excitatory on the damaged side and inhibitory on the healthy side) on the fifth day. The third week proposed conventional rehabilitation care associated with tDCS on both PPC for 5 consecutive days of that week. The assessment (TAP, line bisection test, line crossing test, copying test and questionnaire on activities of daily living) was performed before, just after, at 1 week post-treatment and finally at 1 month post-treatment. Results showed an improvement on the line bisection tasks and copying test after the combined treatment, and also an improvement of the attention parameters, only the latter lingered during the follow-up evaluations. This combined application suggests a potentiation of the improvement effects of conventional rehabilitation care.

6. Perspectives

The use of non-invasive brain stimulation in rehabilitation care management of hemi-spatial neglect seems quite promising in light of these different studies. These investigations must be continued in order to transpose these preliminary data to clinically-relevant effects. Larger controlled, randomized, blinded and prospective studies are needed to achieve this goal.

Furthermore, the association of brain stimulation with specific training paradigms could be proposed to induce sustainable and functionally relevant improvements.

Results from these studies are quite heterogeneous and some methodological issues should be discussed. Hesse et al. [13] underlined some key methodological points.

The choice of evaluation tools to determine the efficacy and clinical relevance of the treatment proposed is an essential prerequisite to compare the different paradigms. The clinical and lesional heterogeneity as well as the different associated deficits should also be considered. Existing studies show quite a diversity in the tests used, and the evaluation of the impact on activities of daily living and the potential transfer to daily life situations are rarely brought up.

The stimulation site, in reference to the anatomical and pathophysiological concepts especially regarding inter-hemispheric competition is an essential element. Both approaches (stimulating the right damaged hemisphere or inhibiting the left healthy hemisphere) have the common objective to reinforce the damaged side and seem quite promising. Precise anatomical landmarks such as functional characteristics of the deficit should in the future be used to define the target zone on an individual scale (i.e. line bisection and PPC, intentional neglect and frontal lobe).

Optimal stimulation modalities (type, intensity, duration and frequency of the sessions) still need to be refined. Repeated sessions seem promising in terms of amplitude and/or duration of the effects, but the long-term effects of repeated sessions, in terms of benefits and safety have rarely been studied.

Ideal post-stroke delay (acute vs chronic state) has not been evidenced yet, whether in terms of effectiveness or harmlessness. To date, the groups of patients studied were quite heterogeneous, beneficial effects were demonstrated both at the sub-acute and chronic phases. The eventual difference in the effect sustainability has not yet been evaluated. Furthermore, most studies have assessed the effects on the short term, since the longest post-treatment evaluation follow-up was 6 weeks.

The choice of patients that could benefit from these techniques must take into account the location and size of the lesion, clinical type, but also eventual contraindications, in order to adapt the treatment to each individual patient. These parameters (mainly lesion site and size) are quite heterogeneous in the various studies reported to date and thus cannot bring an answer to this question.

Combined care management within a neuromodulation approach should be explored. In this context, several parametric elements should be looked at, such as the sequential or simultaneous nature of the combination or the type of associated rehabilitation training (physiotherapy, occupational therapy, more specific approach).

7. Conclusion

A certain number of new approaches have been developed in these past 15 years in the field of hemi-spatial neglect rehabilitation, among them non-invasive brain stimulation [11,47]. Results seem promising even if certain methodological considerations (especially the size of cohorts and blinded conditions) remain insufficient to clearly define their positioning.

Complementary aspects need to be refined in order to propose a more systematic application in daily clinical practice: ideal stimulation protocol, individualization according to the lesion site, intensity, duration and frequency of treatment, post-stroke delay for the beginning of the treatment, combination of approaches, prognostic and effectiveness criteria.

A promising perspective for the future is the combination of several types of approaches in the objective of optimization and/or complementarity: associations (intentional [top-down] and automatic [bottom-up], fast [vestibular stimulation] and slow [prismatic adaptation], lateralized [TMS and tDCS] and global, physical [behavioral and pharmacological]) guided by standardized appropriate evaluations. These seem really relevant in terms of decreasing impairments and promoting functional improvements. This hypothesis becomes even more valid since spatial cognition deficits are quite heterogeneous, and would be greatly facilitated by the improvement of fundamental knowledge on hemi-spatial neglect mechanisms, which could, in the future, guide the choice of the most appropriate treatment(s) for a given patient.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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