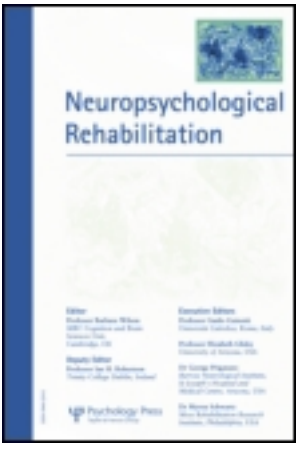

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Ameliorating spatial neglect with non-invasive brain stimulation: From pathophysiological concepts to novel treatment strategies

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Ameliorating spatial neglect with non-invasive brain stimulation: From pathophysiological concepts to novel treatment strategies

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Neglect is a multifaceted, complex syndrome, in which patients fail to detect or respond to stimuli or parts thereof located contralesionally. Non-invasive brain stimulation by means of transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) may not only be useful as diagnostic research tools to explore the pathophysiology of neglect, but also for ameliorating its symptoms. Current approaches for modulating neglect non-invasively are mainly based on the neurophysiological concept of interhemispheric inhibition, which suggests a pathological overactivation of the contralesional hemisphere due to reduced inhibitory influences from the lesioned one. Within this framework, non-invasive brain stimulation mainly aims to inhibit the contralesional hemisphere to allow for rebalancing the system. However, facilitatory protocols for enhancing the ipsilesional neural circuitry might also prove useful. In this review, we discuss the contribution of non-invasive brain stimulation to current pathological concepts of neglect, the promising results of the proof-of-principle studies currently available as well as the specific aspects to be systematically investigated before broader clinical trials may eventually suggest a routine clinical application.

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INTRODUCTION

Starting off as a valuable diagnostic tool in clinical neurophysiology, non-invasive brain stimulation by means of transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) is now – with new stimulation protocols at hand allowing for prolonged effects – at the edge of becoming an adjuvant tool to support recovery of function after stroke (for reviews see Edwards & Fregni, 2008; Harris-Love & Cohen, 2006; Hummel & Cohen, 2006; for methods see Sparing & Mottaghy, 2008). In this review, we focus on the application of these techniques in the context of neglect, a complex, multifaceted multimodal disorder associated with a failure to attend to the contralesional side of space or an object, most commonly observed following right hemisphere damage. Neglect limits the degree of active participation in rehabilitation programmes and is thus associated with poor functional recovery and less successful social reintegration (Arene & Hillis, 2007). In the following we discuss the contribution of non-invasive brain stimulation to the characterisation of the pathophysiology underlying neglect as well as its potential to subserve rehabilitation.

SPATIAL NEGLECT: A MULTIFACETED SYNDROME

Spatial (hemi-)neglect or (hemi-)inattention are clinical terms used to describe a number of different clinical symptoms which have in common the patient's failure to attend, respond adequately, or orient voluntarily to people or objects located at the side of space contralateral to the lesion (Bisiach & Vallar, 2000; Heilman, Watson, & Valenstein, 2003; Husain, 2008; Mesulam, 1981). One particularly interesting feature observed in many cases of neglect is the phenomenon of extinction: Objects or targets may be particularly omitted if stimuli within the ipsilesional space are present that "magnetically" attract attention. Although visuospatial attention is mediated by a widely distributed network of areas in the parietal and frontal cortices of both hemispheres, chronic visuospatial neglect is most reliably observed following lesions in the right hemisphere, and in particular following damage to the posterior parietal cortex (PPC) and the temporoparietal junction (TPJ) (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000; Halligan, Fink, Marshall, & Vallar, 2003; Husain & Nachev, 2007; Mort et al., 2003; Vallar & Perani, 1986). Within the PPC, whether the right

supramarginal gyrus (SMG) (Committeri et al., 2007; Doricchi & Tomaiuolo, 2003; Vallar & Perani, 1986) or the right angular gyrus (ANG) (Hillis et al, 2005; Mort et al., 2003) play a predominant role in the manifestation of neglect is still a matter of debate. Patients with neglect symptoms may not only present with cortical, but also with subcortical stroke. Consistent with previous hypotheses, damage to cortical regions may provoke modular deficits, whereas subcortical lesions may disrupt fronto-parietal connections and affect several cortical modules within a disturbed network, aggravating the clinical presentation (Bartolomeo, Thiebaut de Schotten, & Doricchi, 2007; Doricchi & Tomaiuolo, 2003; Verdon et al., 2010).

Different neuropsychological tests have been applied to test for symptoms of neglect. Traditionally neglect is assessed by the line bisection task, in which lines are typically bisected towards the ipsilesional side, or the length judgement task of pre-bisected lines (also known as the Landmark task), and by various cancellation tasks, scene copying, clock drawing or text reading, in which contralesional targets, object parts or words are omitted. Several dissociations of performance have been described for these tasks (e.g., Binder, Marshall, Lazar, Benjamin, & Mohr, 1992; Halligan & Marshall, 1992; Vallar, 1998). For example, Daffner, Ahern, Weintraub, and Mesulam (1990) reported an interesting case with two sequential focal right hemisphere strokes, the first affecting the right frontal lobe causing motor neglect and the second affecting the right parietal lobe eliciting additional perceptual-sensory aspects of neglect. Likewise, spatial attention within the personal or extrapersonal space may be differentially affected (Committeri et al., 2007; Halligan & Marshall, 1995; Weiss et al., 2000).

Individual reports focusing on different aspects of neglect caused difficulties in finding a clear correspondence between behavioural dissociations and different lesion localisations (Coulthard, Parton, & Husain, 2006). In order to overcome these difficulties, Verdon et al. (2010) used a battery of different clinical tests for a data-driven symptom-lesion mapping. Based on the performance in the individual tests, they identified distinct symptom-profile components related to perceptive/visuospatial, exploratory/visuomotor and allocentric/object-centred aspects of spatial neglect, which mapped to distinct lesion locations, namely the right inferior parietal lobule for the perceptive/visuospatial component, the right dorsolateral prefrontal cortex for the exploratory/visuomotor component, and deep temporal lobe regions for the allocentric/object-centred component.

In general, however, patients with neglect have relatively large lesions, which are likely to disrupt several functional modules. The exact combination of deficits observed in an individual is thus likely to depend upon the extent and distribution of the lesion and its local and distant (i.e., diaschitic) effects (Bartolomeo et al., 2007; He et al., 2007; Verdon et al., 2010). Finally,

compensatory strategies in one domain but not another may add to the multifaceted nature of the syndrome.

NETWORKS OF ATTENTION AND THE CONCEPT OF INTERHEMISPHERIC RIVALRY

Going beyond concepts of localised specialised brain functions and their disturbance due to a focal lesion, neglect is more and more regarded in terms of a dysfunction and disequilibrium of the fronto-parietal networks of attention. Within these networks, spatial attention is controlled by both intra- and interhemispheric connections. Focusing on these aspects, the concept of interhemispheric rivalry originally proposed by Kinsbourne (1977, 1994) suggests that both parietal cortices exert reciprocal interhemispheric inhibition. Damage to the right parietal cortex causes disinhibition and thus pathological over-activation of the left hemisphere, aggravating the bias to attend to the right and hence to neglect the left side (Figure 1).

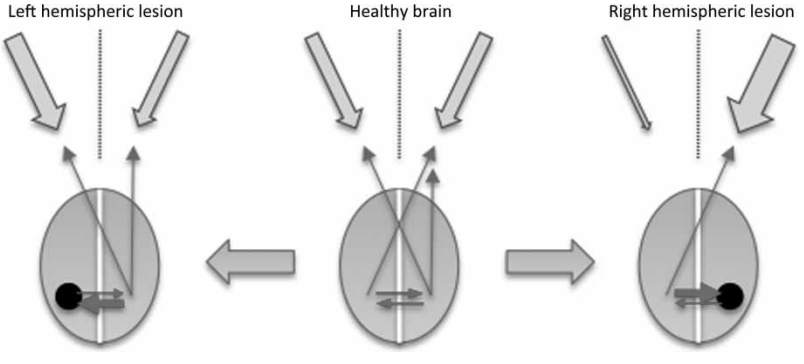

Figure 1. Model of interhemispheric rivalry within a simplified network of spatial attention. A right hemispheric dominance of attention is suggested to explain the predominant occurrence of neglect following right hemispheric lesions. The arrows in front of the head represent visual input, weighted by spatial attention according to their width. *Middle*: In the healthy brain, the left hemisphere directs attention to the right side of visual space (Bisiach & Vallar, 2000; Mesulam, 2002), while the right hemisphere accounts for both sides of space. Interhemispheric connections exert interhemispheric inhibition subserving spatial orientation depending on attentional selection (Rossi & Rossini, 2004). *Left*: Following left hemispheric lesions, the preserved right hemispheric (stimulus-driven) orienting compensates for a diminished voluntary exploration of the right hemispace. *Right*: A right hemispheric lesion results in diminished voluntary orienting towards the contralesional left hemispace in addition to a general lack of stimulus-driven attentional orientation. Interhemispheric inhibition adds to this attentional bias towards the right side of space by disinhibition of the left hemisphere, which in turn causes excessive inhibition from the left to the right hemisphere. [To view this figure in colour, please visit the online version of this journal.]

Recent findings indicate an even greater complexity than originally assigned to this network model, with two complementary networks mediating top-down and bottom-up mechanisms of attention: A bihemispheric dorsal frontoparietal network, including the intraparietal sulcus (IPS), the superior parietal lobule (SPL) and the frontal eye field, which mediates top-down control with voluntary attentional orientation to the contralateral hemispace, and a right-biased ventral frontoparietal network, including the right TPJ, midfrontal gyrus and the inferior frontal gyrus, which responds when behaviourally relevant objects or targets are detected (Corbetta et al., 2000; Corbetta and Shulman, 2002; Hopfinger, Buonocore, & Mangun, 2000). Neglect and its predominant occurrence following right hemispheric lesions may thus be explained by two complementary pathomechanisms: A right hemispheric lesion may result in diminished voluntary orienting towards the contralesional left hemispace in addition to a general lack of stimulus-driven attentional orientation. In contrast, following left hemispheric lesions, the preserved stimulus-driven orienting of attention might compensate for a diminished voluntary exploration of right hemispace. Furthermore, differential effects of lesions affecting the right PPC versus the right TPJ may be envisioned by this model.

Supporting evidence for the basic concept of interhemispheric rivalry stems from clinical observation of a patient who suffered from sequential strokes in both hemispheres with a severe unilateral spatial neglect after a first right-sided parietal infarct (involving the most caudal part of the right angular gyrus) and abrupt disappearance of the neglect after a second left-sided frontal infarct involving the left frontal eye field (Vuilleumier, Hester, Assal, & Regli, 1996). Further evidence supporting the concept of interhemispheric rivalry stems from fMRI showing hyperactivity of the left undamaged hemisphere in neglect patients (Corbetta, Kincade, Lewis, Snyder, & Spair, 2005). The concept of interhemispheric rivalry particularly provides an explanation for the phenomenon of extinction, with simultaneous presentation of a competing stimulus activating the intact hemisphere, thereby leading to a further suppression of the lesioned hemisphere, which reduces the "perceptual weight" of the contralesional stimulus. It also provides the basis for the main strategy of therapeutic non-invasive brain stimulation attempting to countervail this interhemispheric imbalance by inhibiting the over-active contralesional hemisphere, as we will discuss later.

ANIMAL RESEARCH ON NEGLECT

Few studies have used electrical brain stimulation in animal models to identify direct neuronal effects of these techniques on visual attention. Methodological

constraints may account for this, since spatial accuracy of TMS in small animals with standard coils is poor and excessive coil heating may be associated with intensive stimulation. Thus, most important contributions from animal models result from other permanent and/or transient lesion techniques: In 1966 James Sprague published a seminal paper that described a visual recovery phenomenon in the cat that has since been called the "Sprague effect". In cats a large unilateral visual cortical lesion produces an enduring hemianopia (i.e., blindness in half of the visual field). Sprague observed a dramatic recovery of the cat's visual orienting ability to stimuli presented in the previously blind hemifield, when the superior colliculus contralateral to the cortical lesion was ablated. This remarkable observation demonstrated that a second lesion may at least in part counteract the effects of a first lesion and ameliorate symptoms induced by the first lesion. Later studies, using a method of reversible cooling deactivation in cats, could likewise demonstrate that visual neglect, induced by unilateral deactivation of the posterior parietal cortex, could be reversed by additional deactivation of the homologue area of the opposite hemisphere (Lomber and Payne, 1996; Lomber, Payne, Bilgetag, & Rushmore, 2002; Lynch & McLaren, 1989; Payne, Lomber, Rushmore, & Pascual-Leone, 2003; Payne & Rushmore, 2003). Valero-Cabré and coworkers finally succeeded in the development of rTMS and tDCS animal models. Stimulation of the cat parietal cortex modulated visual-spatial processing and induced visuotopically specific neglect-like syndromes using rTMS (Valero-Cabré, Pascual-Leone, & Rushmore, 2008, Valero-Cabré, Payne, & Pascual-Leone, 2007; Valero-Cabré Payne, Rushmore, Lomber, & Pascual-Leone, 2005; Valero-Cabré, Rushmore, & Payne, 2006) as well as using cathodal tDCS (Schweid, Rushmore, & Valero-Cabré, 2008).

INVESTIGATING VISUOSPATIAL FUNCTIONS IN HEALTHY SUBJECTS BY TMS AND tDCS

During the past two decades, the modulation of visuospatial functions by TMS contributed significantly to the refinement of our understanding of the pathophysiology underlying neglect. Researchers made use of the perturbation approach of TMS in order to create "virtual patients", by transiently inducing a neglect-like behaviour in normal subjects (for reviews see Bartolomeo, 2007; Fierro, Brighina, & Bisiach, 2006; Hillis, 2006; Minussi et al., 2008; Pascual-Leone, Walsh, & Rothwell, 2000; Utz, Dimova, Oppenlander, & Kerkhoff, 2010).

Similarly to the diagnostic testing of patients, different tasks were used to define "neglect-like symptoms" in healthy subjects, targeting different cortical areas for stimulation in order to determine those structures actually involved in the respective processing.

Behavioural tasks used to detect neglect-like symptoms

Visual extinction was investigated using a visuospatial detection task with single or bilateral targets presented to the right or left visual hemifield, generally at detection threshold. Decreased detection rates of left targets at bilateral simultaneous presentation were shown following right parietal TMS. This extinction-like phenomenon could be induced using rTMS (Hilgetag, Theoret, & Pascual-Leone, 2001; Jin & Hilgetag, 2008; Pascual-Leone et al., 1994), as well as single pulse TMS (Dambeck et al., 2006; Meister et al., 2006; Müri et al., 2002), but also by tDCS, as demonstrated lately by Sparing and coauthors (2009). Similarly, rTMS of the parietal cortex reduced detection of contralateral somatosensory stimuli at bilateral presentation (Nager, Wolters, Munte, & Johannes, 2004; Seyal, Ro, & Rafal, 1995).

Cued-reaction tasks using valid and invalid spatial cues suggest enhanced engagement as well as a reduced ability to disengage when stimuli are presented in the right hemispace following rTMS over the right parietal cortex, as reaction times to left targets following invalid right cues increased (Chambers, Stokes, Janko, & Mattingly, 2006; Rounis, Yarrow, & Rothwell, 2007; Rushworth, Ellison, & Walsh, 2001; Thut, Nietzel, & Pascual-Leone, 2005). This effect was not accomplished by rTMS over the left parietal cortex (Rushworth et al., 2001) or bilateral dorsolateral prefrontal cortex (DLPFC) (Rounis et al., 2007). Despite the fact that right parietal TMS modulates both visuospatial attention as well as visuospatial detection, these high-level cognitive functions do not seem to share linear or simple relationships, as the decrease in detection rates of masked stimuli and the increase in reaction times to invalidly cued targets did not correlate at the individual level (Babiloni et al., 2007).

Using the line bisection task or the Landmark task (i.e., judgements of pre-bisected lines), a clear rightward bias could be demonstrated following right parietal rTMS (Bjoertomt et al. 2002; Brighina et al., 2002; Fierro et al., 2000), as well as single-pulse TMS (Fierro, Brighina, Piazza, Oliveri, & Bisiach, 2001; Pourtois, Vandermeeren, Olivier, & de Gelder, 2001). Interestingly, using off-line high-frequency, i.e., excitatory, rTMS over 10 minutes before the judgements of pre-bisected lines, Kim et al. (2005) showed facilitative effects on visuospatial attention to the contralateral hemispace bilaterally, but found an inhibitory effect to the ipsilateral hemispace only in the left PPC. Ghacibeh et al. (2007) were able to dissect neglect into visuospatial and motor-intentional components by comparison of parietal and frontal rTMS. Subjects performed a line bisection task with the direct view on the hands precluded while the hand movements were presented on a video screen either in a direct or mirrored fashion. In contrast to right parietal rTMS, rTMS over the right frontal cortex caused a rightward deviation independent of the visual feedback.

To simulate better everyday behaviour, Nyffeler et al. (2008) used a visual exploration task with colour photographs of real-life scenes and monitored eye movements to evaluate attentional deficits as shown in neglect patients. Theta-burst stimulation (TBS), a recent protocol, originally used to induce long-term potentiation or long-term depression in brain slices (Larson, Wong, & Lynch, 1986), applied to the right PPC induced neglect-like behaviour with reduced eye movements and fixations to the left hemispace.

Targeted sites in brain stimulation studies on neglect

Compared to vascular lesions, which are variable in size and location within the vascular territories, TMS is capable of inducing much more focal and consistent lesions, allowing for a more precise mapping of brain function. The inter-individual anatomical differences, however, need to be respected and addressed by appropriate targeting strategies (Sparing, Buelte, Meister, Paus, & Fink, 2008; Sparing, Hesse, & Fink, 2010; Sparing & Mottaghy, 2008).

Most studies demonstrated neglect-like symptoms induced by stimulation of the right PPC. In some of those studies, the left PPC, the occipital cortex, the prefrontal cortex and the superior temporal gyrus (STG) served for control. rTMS over the right dorsal PPC was shown to (1) cause visual extinction (Dambeck et al., 2006; Hilgetag et al., 2001), as well as a rightward bias in a line bisection task (Bjoertomt, Cowey, & Walsh, 2002; Ellison, Schindler, Pattison, & Milner, 2004; Ghacibeh et al., 2007; Oliveri & Vallar, 2009); (2) impair spatial reorientation to invalidly cued left targets (Rounis et al., 2007; Rushworth et al., 2001; Thut et al., 2005); and (3) enhance target detection in the ipsilesional hemispace (Chambers et al., 2006; Hilgetag et al., 2001). The differential roles particularly of the SMG and ANG within the PPC, however, are still a matter of debate: Rushworth et al. (2001) for instance demonstrated that rTMS over the right ANG increases reaction times to invalidly cued left targets with no effect of rTMS over the right supramarginal gyrus SMG, while Oliveri and Vallar (2009) induced a rightward bias in the line bisection task by rTMS over the right SMG, with stimulation over the right ANG as well as STG being ineffective. Most likely these differential results relate to the tasks and functional differences of ANG and SMG, respectively.

Evidence for the concept of interhemispheric rivalry

Apart from the animal and fMRI studies mentioned above, brain stimulation studies also provide evidence supporting the model of interhemispheric rivalry. Enhanced sensitivity and lowered detection thresholds within the hemispace ipsilateral to the stimulation have also been interpreted as being indicative of disinhibition of the contralateral hemisphere (Babiloni et al., 2007; Hilgetag et al., 2001; Seyal et al., 1995). Pathological hyperexcitability of the left hemisphere has recently been shown by a twin coil approach, with a

conditioning pulse over the left PPC prior to the stimulation of the left motor cortex showing an increased left PPC-motor-cortex circuit excitability in neglect patients compared with right hemispheric stroke patients without neglect (Koch et al., 2008).

Most importantly, however, restorative features could be demonstrated in healthy subjects using double stimulation protocols: While confirming extinction-like phenomena following unilateral stimulation applied to the right parietal cortex, Dambeck et al. (2006) as well as Fierro et al. (2006) showed that paired bilateral TMS did not elicit neglect-like deficits in healthy subjects in a cued target-detection or line-bisection task, respectively. Thus, the contralateral pulse restored the neglect-like symptoms induced by the first pulse, most likely by rebalancing the system. Similarly, the initial rightward shift of mean cumulative fixation following TBS over right PPC (Cazzoli, Wurtz, Muri, Hess, & Nyffeler, 2009) could be reversed by TBS of left PPC. Importantly, left PPC stimulation alone had no significant effect on visual exploration. These findings indicate that bilateral inhibition restoring an interhemispheric imbalance ameliorates neglect symptoms.

Protocols used in brain stimulation studies on neglect

Different stimulation protocols have been used to induce neglect-like behaviour. Primarily, in an "on-line" approach, short trains of rTMS over seconds interfered with the neuronal processes underlying spatial processing as long as the targeted cortical area was stimulated (Bjoertomt et al., 2002; Ellison et al., 2004; Fierro et al., 2000; Muggleton et al., 2006; Pascual-Leone et al., 1994; Rushworth et al., 2001). Exploring these issues further, application of single TMS pulses investigated the timing of the underlying attentional processes within individual trials (Fierro et al., 2001; Pourtois et al., 2001). Other studies probed long trains of rTMS over minutes to demonstrate effects on attentional tasks administered immediately after the stimulation had ceased in an "off-line" approach (Hilgetag et al., 2001; Rounis et al., 2007; Thut et al., 2005). Duration of these post-stimulation effects (between 10 and 20 minutes), however, hardly lasted longer than the stimulation itself (between 10 and 25 minutes). The recent protocol of TBS proved capable of inducing longer lasting after-effects (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). With respect to neglect, a TBS protocol consisting of repeated bursts of three pulses at 30Hz repeated over 44 seconds was shown to induce behavioural effects lasting 30 minutes (Nyffeler et al., 2006a). In addition, repeated TBS applications disproportionately prolonged the post-stimulation effects up to 32 hours (Nyffeler et al., 2006b), rendering these protocols more appropriate for putative treatment purposes. Similarly, the after-effects induced by tDCS, which delivers weak direct currents via two electrodes placed on the scalp to polarise neural tissue, are thought to potentially last

up to a few hours (Fregni & Pascual-Leone, 2007; Nitsche & Paulus, 2000; Paulus, 2003; Sparing & Mottaghy, 2008; Wassermann & Grafman, 2005).

Facilitatory vs. inhibitory effects of non-invasive brain stimulation

Depending on the protocol used, brain stimulation may have opposite effects on the underlying brain tissue: low-frequency rTMS (1Hz), continuous TBS as well as cathodal tDCS are assumed to decrease cortical excitability, while high-frequency rTMS (5Hz), intermittent TBS as well as anodal tDCS primarily seem to enhance cortical excitability and thus seem to have facilitatory effects (Hallett, 2007; Nitsche and Paulus, 2000, 2001; Nitsche et al., 2005, 2008; Priori, Berardelli, Rona, Accornero, & Manfredi, 1998; Wagner, Valero-Cabre, & Pascual-Leone, 2007; Vallar & Bolognini, this issue). However, inter-individual variability, as well as state-dependent effects of brain stimulation, challenge this widely held assumption of a clear-cut dichotomy: Cortical preconditioning by rTMS or tDCS showed an enhancement, or even reversal, of inhibitory or facilitatory effects of the succeeding rTMS (Iyer, Schleper, & Wassermann, 2003; Siebner et al., 2004; Silvanto & Pascual-Leone, 2008). These findings point to the importance of taking the status of the targeted tissue into closer consideration, which should particularly apply for lesioned tissue following stroke.

NEUROREHABILITATIVE APPROACHES IN NEGLECT PATIENTS BY MEANS OF TMS AND tDCS

Based on the model of interhemisheric rivalry and the availability of facilitatory and inhibitory protocols, basically two approaches to use non-invasive brain stimulation in neglect patients are conceivable: Inhibiting the contralesional hemisphere and enhancing the lesioned hemisphere (Figure 2A). Most studies thus far have aimed to inhibit the contralateral hemisphere, more specifically, based on evidence for a central role of right parietal cortex in neglect, the left parietal cortex. These studies indeed affirmed that inhibitory rTMS of the unaffected left parietal cortex transiently improves contralesional visuospatial neglect and extinction (for an overview, see Table 1). However, previous TMS/rTMS studies on patients did not directly compare "inhibitory" and "facilitatory" stimulation protocols. In contrast, using tDCS, Sparing and co-authors (2009) observed a clear interaction between stimulation side and type of stimulation with both contralesional inhibition as well as ipsilesional facilitation ameliorating neglect symptoms (see Figure 2B). Ko and co-workers (2008) also demonstrated an enhancement of performance resulting from a "facilitatory" stimulation of the lesioned cortex in neglect patients. While for obvious reasons fully restoring functions of the lesioned site seems out of reach, facilitating protocols

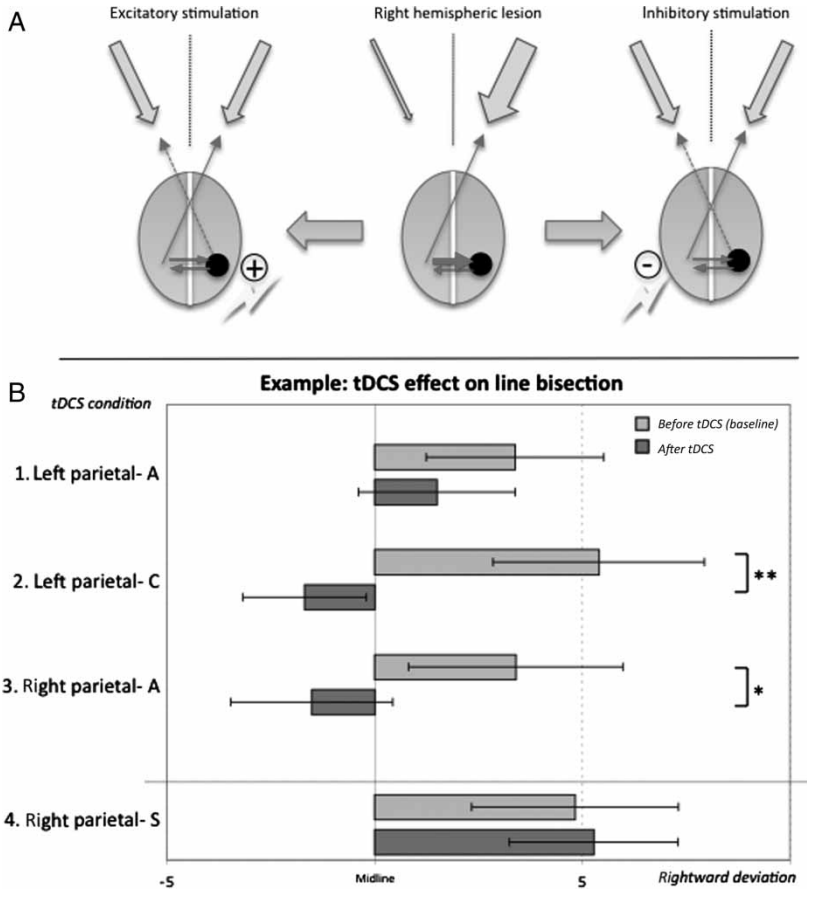

Figure 2A. Model of effect of non-invasive brain stimulation on brains with right hemispheric lesions. The arrows in front of the head represent visual input, weighted by spatial attention according to their width. *Middle*: A right hemispheric lesion causing diminished voluntary and stimulus-driven orienting towards the contralesional left hemispace, with interhemispheric inhibition enhancing this attentional bias. *Left*: Facilitating right parietal stimulation augments activity of the right hemisphere, increasing interhemispheric inhibition from the right to the left hemisphere and thereby rebalancing the interhemispheric interactions. *Right*: Inhibitory left parietal stimulation releases the right hemisphere from excessive inhibition by the left hemisphere, thus reconstituting interhemisphere balance of attentional networks. **2B.** Results adapted with permission from Sparing et al. (2009). Neglect patients were tested with a computerised line bisection task. In all four baseline conditions (bars in light grey), patients showed a rightward deviation reflecting left hemispatial neglect. Both, $tDCS_{anodal}$ of the lesioned (right) hemisphere (3), and $tDCS_{cathodal}$ of the unlesioned (left) hemisphere (2), caused a significant reduction in the rightward bias (mm). No significant modulatory effect on deviation was observed following $tDCS_{anodal}$ of the unlesioned hemisphere (1), or $tDCS_{sham}$ (4). A = $tDCS_{anodal}$; S = $tDCS_{sham}$; C = $tDCS_{cathodal}$. $^{**}p < .01$, $^{*}p < .05$. [To view this figure in colour, please visit the online version of this Journal.]

TABLE 1
Studies currently available evaluating the effects of TMS/tDCS in neglect patients

			Protocol /technique	*Subjects*	*Time post stroke*	*Targeted region*[1]	*Main experimental task (test dates)*	*Main results*
TMS	On-line	Oliveri et al., 1999	Single-pulse TMS 4 sessions (4 target regions) fig-of-eight coil, 110% MT	14 patients right BD (8 visuospatial hemineglect; 6 contralat. somatosensory deficits)	1-4 months	Frontal cortex (F3, F4), parietal cortex (P3, P4)	Discrimination of electrical tactile stimuli (on-line)	Left frontal TMS reduces contralesional extinction in patients with unilateral right brain damage
		Oliveri et al., 2001	25 Hz rTMS; trains of 10 pulses, fig-of-eight coil, 115% MT	5 patients right BD (1 P, 1 F, 1 F-T, 2 P-T lesion); 2 patients left BD (1 P-T, 1 F-P-T lesion)	1 to 48 weeks	Right / left parietal cortex (P5, P6)	Length judgement of prebisected lines (on-line)	rTMS of the unaffected hemisphere transiently decreased the magnitude of neglect
	Off-line, single session	Koch et al., 2008	1 Hz rTMS; 600 pulses, fig-of-eight coil, 90%/ 110% MT (Exp.1: twin-coil TMS; Exp.2: rTMS+twin-coil)	12 patients right BD (for lesion maps see original paper)	4 to 24 weeks	Left parietal cortex (P3), left motor cortex (M1) defined by TMS mapping	Measurement of MEP amplitude, naming of visual chimeric objects pre, post)	Neglect symptoms as well as pathological hyperexcitability of left PPC-M1 circuits (correlating with degree of neglect on clinical cancellation tests) are reduced following 1 Hz rTMS
		Nyffeler et al., 2009	Continuous TBS (801 pulses in 267 bursts of 3 pulses at 30 Hz, interburst interval 100 ms; 2 (or 4) trains of 44s in one session at 0, 15 (& 60, 75) min. round coil, 100% MT	11 patients right BD for lesion maps see original paper)	2 weeks to 36 months	Left parietal cortex (P3), control: no stim., sham stimulation over vertex	Subtest of the Vienna Test System (2xTBS: pre, +1, 8h; 4xTBS: pre, +1, 3, 8, 24, 32, 96h)	Two TBS trains increased detection rate of and reduced reaction times to left targets for up to 8 hours. 4 TBS trains showed same effect for up to 32 hours, effect declines after 96h.
	Off-line, multiple session	Brighina et al., 2003	1 Hz rTMS; 900 pulses, 7 sessions (every other day) over 14 days, fig-of-eight coil, 90% MT	3 patients right BD (2 T-P, 1 F-P lesion)	3 to 5 months	Left parietal cortex (P5)	Length judgement of prebisected lines, line bisection, clock drawing (-2wks, pre, post, +2wks)	rTMS induced a significant improvement of visuo-spatial performance that remained quite unchanged after 15 days

(*Continued*)

Table 1. Continued.

	Protocol /technique	*Subjects*	*Time post stroke*	*Targeted region*[1]	*Main experimental task (test dates)*	*Main results*
Shindo et al., 2006	0.9 Hz rTMS; 900 pulses, 6 sessions within 14 days, fig-of-eight coil, 95% MT	2 patients right BD (1 F-P, 1 P-T)	6 months	Left parietal cortex (P5)	Subtests of the Behavioural Inattention Test (BIT) (-2wks, -1d, +1d, +2wks, +4wks, +6wks)	rTMS decreased unilateral spatial neglect for at least 6 weeks
Song et al., 2009	0.5 Hz rTMS; 450 pulses, 2 sessions each day over 14 days,	7 patients right BD (very heterogenous group)	3 to 8 weeks	Left parietal cortex (P3)	Line bisection and line cancellation tests (-2wks, pre, post, +2wks)	rTMS improved visual spatial neglect in both tests up to 14 days after treatment
Lim et al., 2010	Fig-of-eight coil, 90% MT 1 Hz rTMS; 900 pulses, 5 days/week for 2 weeks,fig-of-eight coil, 90% MT	7 patients right BD for lesion maps see original paper)	1 to 44 weeks	Left parietal cortex (P5)	Line bisection, Albert test (line cancellation) (-1d, +1d)	rTMS improved performance in line bisection test, but not line cancellation at end of treatment

targeting the lesioned hemisphere may still contribute to the amelioration of neglect. Whether this effect may be best achieved by direct enhancement of attention-mediating right hemispheric structures or interhemispheric inhibition on the contralesional cortex remains to be investigated.

Table 1 provides an overview of the studies currently available on non-invasive stimulation in the treatment of neglect. Studies vary with respect to many issues: Oliveri et al. studied on-line effects of single pulse (1999) as well as repetitive TMS (2001), on bilateral parietal cortex, while all other studies assessed off-line after-effects. Koch et al. (2008) demonstrated a reduction of neglect symptoms directly after a single session of rTMS along with the normalisation of a pathologically increased left PPC-M1 circuit excitability as assessed in a double stimulation approach. Using a new TBS stimulation protocol, Nyffeler, Cazzoli, Hess, and Muri (2009) pursued after-effects of two or four TBS trains vs. sham stimulation and control for up to 8 (2 x TBS) or 96 hours (4 x TBS). They showed an increased detection rate for stimuli presented in the left hemispace along with reduced reaction times for up to 32 hours following four TBS trains. Four further studies showed positive effects of multiple sessions of inhibitory low frequency rTMS over a period of two weeks with frequency of treatment ranging from three sessions per week to twice a day (Brighina et al., 2003; Lim, Kang, & Paik, 2010; Shindo et al., 2006; Song et al., 2009). Neglect symptoms were assessed prior to as well as after the period of intervention, without intermediate testing following individual sessions. Finally, two studies investigated the effects of single tDCS sessions showing improved figure cancellation and/or line bisection immediately after ipsilesional anodal and/or contralesional cathodal tDCS (Ko et al., 2008; Sparing et al., 2009).

Reviewing the findings of these heterogeneous studies currently available, some important methodological issues of therapeutic TMS/tDCS studies in visuospatial neglect become obvious, which we discuss below.

METHODOLOGICAL KEY POINTS

How to determine efficacy and clinical relevance of the treatment

As discussed above, neglect is a heterogeneous disorder with varying clinical presentations, lesion location and size of lesion. With inconsistent correlations of performance in different tests, it seems a challenging task to reliably measure the effects of neurorehabilitation and its impact on daily living. The studies listed in Table 1 showed improvements in different tasks used to survey the course of the treatment or individual treatment sessions. Interestingly, Sparing et al. (2009) as well as Lim et al. (2010) were able to detect significant behavioural changes in one test, the line bisection task, following

tDCS or rTMS, but not in the other (TAP task or line cancellation, respectively). How should we deal with dissociations of treatment effects, which may reflect the interindividual diversity of the neglect syndrome due, for instance, to different lesion sites affecting different cognitive domains (Marshall & Halligan, 1995; Vallar, 1998)?

Even less clear is the question of how individual performance in neuropsychological tests relates to the patients' deficits in their activities of daily living – and thus how to extrapolate the effect of brain stimulation on daily living from those test results. Although the presence of neglect is well known to affect the outcome of rehabilitation, the exact impact of neglect as such on the patients' daily life is hardly examined – partially due to a lack of adequate tests (Eschenbeck et al., 2010).

In addition to its diversity, neglect generally does not present on its own, but is often associated with somatosensory deficits, hemiparesis, hemianopia or anosognosia. Depending on lesion size and location, the combination with other neurological deficits may not simply add up but disproportionately potentiate thereby affecting or even limiting the rehabilitative potential of non-invasive stimulation. A special problem in this vein may be imposed by the additional presence of hemianopia. Dissociating true hemianopia, i.e., primary visual field defects, from pseudo-hemianopia induced by neglect is not an easy task and hardly feasible during a standard neurological examination. Electrophysiological examination may show normal visual evoked potentials in such patients (Vallar, Sandroni, Rusconi, & Barbieri, 1991), indicating intact primary visual processing. Specific neuropsychological testing may reveal that the visual field defect vanishes when the gaze is directed towards the right side (Kooistra & Heilman, 1989), indicating a pseudo-hemianopia related to neglect only. However, if both deficits are present, the coincidence of left unilateral spatial hemineglect and homonymous hemianopia evokes an even more severe inattention to the left side (Cassidy, Bruce, Lewis, & Gray, 1999). Zihl (1995) reported that 60% of their patients with homonymous hemianopia, but without signs of neglect, had impaired visual scanning behaviour. The presence of additional deficits thus needs to be taken into account when determining an accomplishable goal as well as when judging the effectiveness of the treatment.

Where to stimulate? Anatomy, pathophysiological concepts and neuronavigation

Consistent with the classic concept of hemispheric rivalry originally proposed by Kinsbourne (1977, 1994), the available results of TMS and tDCS studies performed in the context of neglect and spatial processing suggest that both targeting the intact left hemisphere with inhibitory as well as the lesioned right hemisphere with facilitatory stimulation protocols are promising. Both

approaches aim at "strengthening" the right hemisphere. Supposing that interhemispheric rivalry indeed exists, and that it exerts its effect upon corresponding bi-hemispheric locations, left hemispheric stimulation should target structures corresponding to neglect-defining structures in the right hemisphere. Hence, thus far, PPC was the primary target of stimulation in all studies.

Future protocols might aim at individually adapting the site of stimulation to the structures affected, rather than using a single target location for all neglect patients. Anatomical landmarks of the lesion or functional characteristics of the deficit may be used to define the individual target area. For example, line bisection, repeatedly shown to draw upon PPC along the IPS (Fink et al., 2000, 2003; Fink, Marshall, Weiss, & Zilles, 2001), improved with PPC stimulation (Lim et al., 2010; Sparing et al., 2009). Thus the site of stimulation may determine which component of neglect is modulated. Patients with intentional neglect, inducible by frontal rTMS, might benefit from frontal stimulation (Ghacibeh et al., 2007). Whether targeting other structures within the frontoparietal networks is similarly effective has not yet been studied.

From a theoretical point of view, more sophisticated network models of attention accounting for neglect symptoms need to be incorporated into the classic concept of hemispheric rivalry. One might hypothesise that the concept of interhemispheric rivalry applies well to the bilaterally distributed dorsal frontoparietal network of voluntary top-down attention. Whether it similarly suits the right biased ventral frontoparietal network of bottom-up orientation has not yet been investigated.

The precise and reliable localisation of the target area is not a simple task either. Regarding a functional approach, TMS outside the motor and visual cortex does not result in an overt response such as muscle twitches or visual sensations (i.e., phosphenes). Nevertheless, feasible "hunting" methods for the IPS or ANG have been proposed by Oliver, Bjoertomt, Driver, Greenwood, and Rothwell (2009) and Göbel, Walsh, and Rothworth (2001), showing specific localised disruptive effects of rTMS on a visuospatial or number comparison task, respectively. For the lesioned, and, therefore, malfunctioning hemisphere, however, hunting procedures may be less reliable. Spatial tracking of the target area by the International 10–20 EEG system relies on cranial landmarks (e.g., nasion, inion, and preauricular points), but does not allow to account for interindividual neuroanatomical differences (Binnie, Dekker, Smit, & Van der Linden, 1982; Myslobodsky, Coppola, Bar-Ziv, & Weinberger, 1990) resulting in interindividual variations in electrode position up to the range of 20 mm (Herwig, Satrap, & Schönfeldt-Lecuona, 2003). Optically tracked frameless stereotaxic neuronavigation systems, which incorporate individual MRI data, provide an alternative means to tackle this problem, allowing for an accuracy within the

millimetre range (Sack et al., 2009; Schönfeldt-Lecuona et al., 2005; Sparing & Mottaghy, 2008; Sparing et al., 2010).

On the other hand, high focal precision may not be a desirable goal for therapeutic stimulation. Circumscribed application may have focused effects, which may prove less suitable for covering the aspect of disturbed neural networks underlying the neglect syndrome. This might generally speak in favour of a more extended area upon which stimulation exerts its effects, possibly favouring the use of tDCS as a less focal method (see also Vallar and Bolognini, this issue). In Sparing et al.'s study (2009), the stimulation area may not have been sufficiently large to cover the full range of neglect symptoms, as suggested by the fact that TAP test performance was not improved by tDCS. Size of lesion correlated negatively with the effect of treatment. While larger lesions generally go along with more severe deficits and less rehabilitative potential, a disadvantageous ratio between lesion size and the area which may be targeted by the stimulation may additionally influence effectiveness of stimulation.

How to stimulate? Intensity, duration or frequency of stimulation sessions

Stimulation protocols and individual parameters such as stimulation intensities are usually derived from neurophysiological studies of motor cortex excitability. Optimal stimulation parameters for non-motor areas are presently unknown. With respect to treatment effects, dose-finding studies varying systematically intensity and duration of stimulation or frequency of sessions have not been conducted thus far. Likewise, cumulative effects of multisession TMS have scarcely been investigated systematically. The four multisession rTMS treatment studies on neglect neither assessed neglect symptoms after individual sessions nor varied treatment duration. Therefore, at present no conclusions on the cumulative nature of the effects can be drawn. Nyffeler et al. (2009) showed that four vs. two TBS trains applied within 75 and 15 minutes, respectively, significantly increased the number of perceived left visual targets along with decreased reaction times for up to 32 vs. 8 hours. However, while the effect of four TBS trains was observed to decline 96 hours after stimulation, the persisting effect of two consecutive TBS trains had not been followed-up beyond 8 hours. In an rTMS study on cats, Valero-Cabré and co-authors (2008) demonstrated that a series of rTMS sessions on consecutive days over the right parietal cortex progressively induced visuospatial neglect-like after-effects of greater magnitude and spatial extent, without prolonging the duration of the effect, suggesting an increased facilitation to subsequent TMS-induced disruptions, but no accumulation. Comparison between effects of multi-session rTMS and TBS, as well as between humans and cats, may not be permitted, and benefits

on injured brains may vary from short to long-term effects of disturbance on intact neuronal systems. It is conceivable that the healthy brain may resist or overcome the induced disturbance of balance with the effects lacking or wearing off over time, while dysbalanced networks in a lesioned brain may be rebalanced. In addition, we envision that an unbalanced network in the lesioned brain (temporarily) overcoming its unbalance by neurostimulation may try to stabilise the induced balanced status.

Indeed, normalisation of over-excitability of the left PPC-M1-circuitry was specific for neglect patients; no change in excitability was observed in the control group of right hemispheric patients without neglect (Koch et al., 2008). In the four multisession studies presented, treatment continued over two weeks. Whether patients would benefit from a longer treatment cycle or a second cycle after a pause remains to be elucidated. Finally, preconditioning of brain tissue by preceding TMS (Iyer et al., 2003) or tDCS (Lang et al., 2004; Siebner et al., 2004) may open up further avenues for future stimulation protocols worth investigating.

Along with the development of treatment protocols, putative adverse effects and risks of the use of rTMS and tDCS should also be assessed carefully. The dosage should generally be limited according to published safety guidelines (e.g., Nitsche et al., 2003; Poreisz, Boros, Antal, & Paulus, 2007; Wassermann et al., 1996). Although current data do not hint at adverse side effects, the particular risks of repetitive stimulation sessions as well as novel protocols such as TBS (Huang et al., 2005) or combinations with pre-conditioning TMS (Iyer et al., 2003) or tDCS (Lang et al., 2004; Siebner et al., 2004) should be concurrently addressed in future investigations.

When to intervene? Acute vs. chronic stage

Another concern is whether stimulation protocols should start in the acute phase, i.e. within the first few days following the onset of stroke, or later. Groups of patients are heterogeneous (see Table 1), also with respect to the time point of stimulation following stroke onset, showing positive effects of stimulation both in the subacute and chronic phase of stroke. Whether the extent of short-term effects differ when applied in the acute compared with the chronic phase has not been investigated systematically. Moreover, long-term treatment and long-term effects studied so far were limited to a period of 6 weeks (Shindo et al., 2006), with most studies only testing for short-term effects.

Current studies do not suggest any negative effects of stimulation depending on the stage of the disease. However, systematic studies are lacking that investigate whether acutely damaged and vulnerable tissue, in particular any tissue at risk at the borders of the lesion, reacts differently to stimulation. Furthermore stimulation protocols should not inhibit adaptive processes prone to

restore the affected neural networks. Finally, patients should not only benefit from early stimulation protocols, but any benefit achieved should be long-lasting and not reachable to the same degree by the same therapy starting at a later time point in order to justify a very early onset of the treatment. If any maladaptive processes resulting from interhemispheric disinhibition should prove irreversible, one might postulate a preventive effect of early-onset stimulation therapy, which could not be regained at later time-points. To the best of our knowledge, these aspects have not been investigated.

Whom to treat? Considering lesion location, size and clinical presentation

Likewise, whether lesion location or size may predict who will or will not benefit from brain stimulation in order to allow for categorising patients and adapting treatment to the individual needs has not been investigated systematically. Patient groups reported are usually very heterogeneous as far as lesion size and location is concerned (see Table 1). Sparing et al. (2009) demonstrated a negative correlation of stimulation effect with lesion size indicating that those patients with larger lesions improve less. Apart from this finding, only four out of the 10 stimulation treatment studies with neglect patients report lesion maps and lesion size or volume – without striving for any correlation with treatment effects. In order to demonstrate a robust effect, however, selection of patient groups seems important: In comparison to more homogeneous groups of healthy individuals, stimulation induced much more variable behavioural effects in patients.

What to add to stimulation? Combination with rest, physical and/or occupational therapy

This aspect addresses the setting in which a neuromodulatory approach may be embedded. Again, this issue has not been explored. Should stimulation be applied separately or can its effects be enhanced when combined with physical or occupational therapy? If a combination is favourable, should stimulation be simultaneous to other treatment, or rather following or preceding it? In other words, should stimulation take place during rest or in combination with certain tasks? If the latter was the case, which tasks would be best suited to enhance the stimulation effect? The demonstration of state-dependent effects of stimulation (Silvanto, Muggleton, & Walsh, 2008, Silvanto & Pascual-Leone, 2008) suggests that these aspects may indeed be relevant.

In a study by Song et al. (2009) all patients were given conventional rehabilitation treatment, while the treatment group also received inhibitory rTMS applied to the left parietal cortex, unrelated to treatment, for 14 consecutive days twice a day for 15 minutes. Only the rTMS treatment group improved in both the line bisection as well as the line cancellation task. In a different

study by Lim et al. (2010), patients received a session of 1 Hz rTMS applied to the left parietal cortex, immediately prior to the 30-minute session of occupational therapy for a total of 10 days within a 14-day period. Six out of 7 patients of the combined treatment group improved with respect to the line bisection task (compared to 2 out of 7 in the control group), however, there is no comment on whether improvements correlated with any parameter reflecting activities of daily living.

CONCLUSION

The currently available proof-of-principle studies of non-invasive brain stimulation in the treatment of neglect give rise to optimism for applying neuromodulatory approaches in the rehabilitation of a so far quite daunting condition. Other therapeutic approaches, such as spatial training, prism adaptation (Fortis et al., 2010), pharmacological treatment (for review see Sivan, Neumann, Kent, Stroud, & Bhakta, 2010) or neck vibration (for reviews for the main approaches see Kerkhoff, 2003; Pizzamiglio, Guariglia, Antonucci, & Zoccolotti, 2006; Rode et al., 2006), also show encouraging effects. Particularly appealing for the brain stimulation approach is, however, the hypothesised pathophysiological concept of hemispheric rivalry, for which current findings provide compelling evidence. Along with functional topography of subcomponents of neglect to be refined by future investigations, more sophisticated network models of attention should be incorporated into the concept of hemispheric rivalry. Finally, larger double-blind, placebo-controlled trials are needed, that systematically study optimal stimulation protocols, possibly individualised for site, intensity, frequency, and duration of stimulation, onset of treatment, co-therapy, and prognostic criteria, before any systematic application in the clinical routine may be pursued. Tackling those aspects, non-invasive brain stimulation may not only excite the so-far very limited treatment options of neglect, but conversely, neglect may also provide a stimulating example of where therapeutic application of non-invasive brain stimulation may be heading in the future.

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