Graduate School of Systemic Neurosciences
LMU Munich

Neuroanatomy and Rehabilitation of the Directional Motor Deficits associated with Unilateral Neglect

Dissertation der

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Submitted by

Maria Gutierrez-Herrera

Munich, 19 March 2018

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ABSTRACT

A growing body of evidence suggests that depending on the presence of certain brain-lesions, patients with unilateral neglect might exhibit directional motor deficits affecting the planning and execution of contralateral movements. However, studies examining the neuroanatomical basis of these deficits report seemingly contrasting findings concerning the participation of frontal and parietal brain areas. Moreover, clinical studies assessing the effectiveness of different therapeutic interventions in the treatment of unilateral neglect indicate that the presence of directional motor deficits seems to contribute to the efficacy of prism adaptation. Nevertheless, considerable debate remains as to whether additional aspects dealing with neuroanatomy and behavior might also determine the influence of this intervention in patient's successful recovery. Considering the importance of identifying the neuroanatomical underpinnings of directional aiming movement, while at the same time shedding light on the mechanisms behind prism adaptation, this thesis combines experimentally- and clinically-oriented research studies. Part of the motivation of these projects is expressed in an opinion article (Chapter 2) which provides some insights into the clinical and therapeutic implications of assessing and carefully examining directional motor deficits.

The first study (Chapter 3) used transcranial magnetic stimulation to elucidate the participation of right angular and middle frontal gyri in the planning and execution of contralateral aiming movements. This study indicated that applying repetitive transcranial magnetic stimulation to the former gyrus affected the initial selection of contralateral movements, whereas stimulating the latter one interfered with control processes required to maintain the goal and commit to the decision to move toward the contralateral side under conditions of high sensory uncertainty.

The second study (Chapter 4) employed a two-week protocol of prism adaptation together with a lesion analysis to explore behavioral and neuroanatomical aspects influencing the effects of this intervention in the initial response and lasting improvement of patients with unilateral neglect. This study revealed that the magnitude of the proprioceptive after-effect correlated significantly with patients' improvement until the follow-up session in neuropsychological tasks with a high motor involvement. Furthermore, it was observed that patients showing a lower prism-related improvement in these tasks had lesions in temporo-parietal areas, whereas those with predominant lesions in frontal and subcortical areas exhibited a higher improvement.

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General Introduction

Our natural ability to interact with the space around us as a unified and coherent whole depends on complex neural mechanisms dealing with spatial representation and attention processes. If these mechanisms break down as a result of right brain damage, a neurocognitive disorder known as unilateral neglect (UN) may arise. In addition to the well-documented deficits in attending to contralesionally located stimuli, patients with UN might also exhibit difficulties in planning and executing movements toward the contralesional side of space. A growing body of evidence suggests that such directional motor deficits (DMD) differ from attentional deficits in terms of their neuroanatomical substrates (Ghacibeh, Shenker, Winter, Triggs, & Heilman, 2007; Sapir, Kaplan, He, & Corbetta, 2007; Vossel, Eschenbeck, Weiss, & Fink, 2010). Moreover, there is indication that a careful assessment of these deficits might be relevant for understanding the effects of a promising therapeutic intervention in UN, called prism adaptation (PA)**.** More specifically, it has been shown that exploratory motor behavior (also termed intentional or aiming behavior) directed toward the contralesional side of space, seems to be predominantly responsive to the influence of PA (Chen, Goedert, Shah, Foundas, & Barrett, 2014; Fortis, Chen, Goedert, & Barrett, 2011; Fortis, Goedert, & Barrett, 2011; Striemer, Russell, & Nath, 2016). This introduction is divided into three parts. The first part gives a general overview of the prevalence, clinical manifestations and neuroanatomical basis of UN, with a special emphasis on DMD and the different techniques employed for their study. The second part focuses on PA and its general contribution to neglect improvement. It also addresses PA's particular influence on the contralateral movement aspects of neglect, as well as the behavioral and neuroanatomical factors associated with such an influence. Finally, the third part outlines the aims of this thesis.

1.1 Prevalence and clinical manifestations of unilateral neglect

Unilateral neglect (UN), also referred to as hemineglect or hemispatial neglect, is a disabling neurocognitive disorder characterized by the inability to spontaneously detect, respond or orient toward stimuli located in the contralesional side of space using either the eyes or the limbs. By definition, such an inability cannot be attributed to primary sensory (i.e. hemianopia, hemianesthesia) or motor deficiencies (i.e. hemiplegia, hemiparesis) (Heilman, Valenstein, & Watson, 1984). These deficiencies might however occur with UN, often being hardly distinguishable from it. Among other clinical manifestations, a typical patient with UN may collide with objects on the ignored side when walking or navigating with the wheelchair; eat food only from one side of the plate; shave, dress or groom only one side of their body; and/or omit words when reading text on one side of the page. These behaviors certainly have a negative impact on patient's ability to function independently in daily life activities, thus supposing a great burden for caregivers and relatives. Moreover, this disorder has been associated with poor functional prognosis (Di Monaco et al., 2011; Katz, Hartman-Maeir, Ring, & Soroker, 1999), decreased likelihood of rehabilitation success (Shulman et al., 2015), and longer hospitalization periods (Gillen, Tennen, & McKee, 2005).

Although the occurrence of UN is attributed to pathological processes such as neurodegenerative diseases (Andrade et al., 2010; Kleiner-Fisman, Black, & Lang, 2003; Silveri, Ciccarelli, & Cappa, 2011), neoplasias (Jackson, 1876), and traumatic brain injury (e.g. La Pointe & Culton, 1969), stroke is known as the most common underlying cause (e.g. Leśniak, Bak, Czepiel, Seniów, & Członkowska, 2008; Stone, Halligan, & Greenwood, 1993). It is estimated that nearly 50% of right hemisphere stroke survivors (Buxbaum et al., 2004; Ringman, Saver, Woolson, Clarke, & Adams, 2004) may exhibit symptoms of unilateral neglect, which in approximately 37% of the cases may persist chronically (e.g. Azouvi et al., 2002; Farnè et al., 2004). Such symptoms have also been reported in patients with left hemisphere stroke, yet with lower incidence rates and severity, and with shorter duration (Ringman et al., 2004; Stone et al., 1993). A model suggesting that the right-hemisphere is specialized for spatial attention generally accounts for this hemispheric asymmetry. In keeping with this model, the left hemisphere is thought to deploy attentional resources chiefly to the contralateral side of space, with the right hemisphere deploying them toward both sides of space (Mesulam, 2002). This difference explains that, with no chance of compensation through left-hemisphere's function, right-hemisphere lesions result in severe left neglect deficits. Since the studies of the current thesis examine the participation of the right hemisphere in this disorder, the terms "neglect" or "UN" will henceforward refer to left-sided manifestations.

1.2 Subtypes and dissociations of neglect symptoms

UN involves a numerous and heterogeneous group of symptoms which may combine and manifest differently across patients. Many subtypes and dissociations have been described according to different aspects of the disorder (e.g. modality, reference frame, and range of space). Based on the modality, neglect is divided into input and output subtypes. The input subtype pertains to sensory deficits affecting the awareness of tactile, auditory, and/or visual stimuli presented in the contralesional side of space. Interestingly, this unawareness might also affect internally generated representations of visual images, thus resulting in representational neglect. The output subtype, on the other hand, is further subdivided into motor and premotor neglect categories (Robertson & Halligan, 1999). Motor neglect relates to the reduced spontaneous utilization of the contralesional limbs in the absence of neuromuscular weakness or sensory loss. Premotor neglect, on the other hand, affects the planning and execution of movements performed with the ipsilesional limb toward the contralesional side of space (Vallar, 1998). Furthermore, neglect symptoms may arise within an egocentric (viewer-centered) and/or an allocentric (object-centered) frame of reference. Patients with egocentric neglect have difficulties attending to stimuli located to the left side relative to the mid-sagittal plane of their body, whereas those with allocentric neglect might not be able to attend to the left side of an object regardless of its position relative to their body (Ting et al., 2011; Vallar, 1998). In addition, according to the range of space, neglect symptoms might affect the subject's own body space or personal space (combing, grooming, and shaving), the space within arm's reach or peripersonal space (eating and reading), and/or the space beyond arm's reach or extrapersonal space (walking and wheelchair navigation) (Ting et al., 2011; Vallar, 1998).

Furthermore, UN can occur in combination with other related impairments, including anosognosia (unawareness of the deficits), anosodiaphoria (indifference to the disabilities), and extinction (failure to report a contralesional stimulus only in the presence of a competing ipsilesional stimulus). Also there is evidence that non-lateralized deficits involving selective attention, sustained attention, and working memory may coexist with this disorder (Husain, 2005).

1.3. Neuroanatomical bases of unilateral neglect

Along with the multiple behavioral manifestations described above, many different brain areas have been shown to play a role in UN. Some of the cortical areas reported to date include the temporo-parietal junction (Heilman, Watson, Valenstein, & Damasio, 1983; Vallar & Perani, 1986), supramarginal (Doricchi & Tomaiuolo, 2003) and angular gyri (Hillis, 2005; Mort et al., 2003), superior temporal gyrus (Karnath, Ferber, & Himmelbach, 2001; Karnath, Berger, Küker, & Rorden, 2004), as well as middle and inferior frontal cortices (Heilman & Valenstein, 1972; Husain & Kennard, 1997). Additionally, at the subcortical level, the thalamus (Cambier, Masson, Graveleau, & Elghozi, 1982; Ringman et al., 2004; Vallar & Perani, 1986; Watson & Heilman, 1979) and the basal ganglia (Ferro, Kertesz, & Black, 1987; Karnath et al., 2004; Ringman et al., 2004; Vallar & Perani, 1986) have been implicated (Figure 1). As a result of these varied findings, a great deal of controversy has surrounded the precise anatomy of neglect. One particular controversial aspect has to do with the involvement of the right inferior parietal lobe (IPL) on the one hand, and of the superior temporal cortex on the other hand. Whereas a number of studies have indicated that damage to the former might be crucial to elicit symptoms of neglect (e.g. Hillis, 2005; Mort et al., 2003; Vallar & Perani, 1986), other studies have pointed to the latter as being more important (e.g. Karnath et al., 2001; Karnath et al., 2004). Among other causes, this conflict might have resulted from the inclusion of different types of patients as well as from the employment of distinct diagnostic tools (e.g. Milner & McIntosh, 2005). As an illustration, the first group of studies included line bisection tasks as part of the assessment, while the second group only applied cancellation tasks. There is evidence that line bisection and cancellation tasks depend, respectively, on posterior parietal and middle temporal areas (Rorden, Fruhmann Berger, & Karnath, 2006; Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2010).

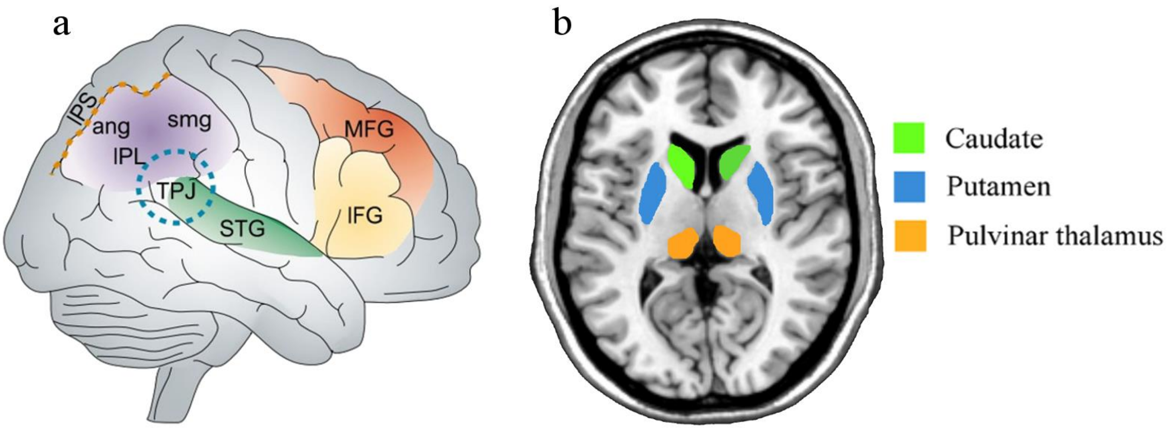

Figure 1. Neuroanatomy of unilateral neglect. a. Cortical regions damaged in patients with unilateral neglect. Posterior regions include the temporo-parietal junction (TPJ), the inferior parietal lobe (IPL) encompassing the angular (ang) and supramarginal gyrus (smg), the intraparietal sulcus (IPS), and the superior temporal gyrus (STG). Frontal areas include the middle frontal gyrus (MFG) and the inferior frontal gyrus (IFG) (adapted from Husain, 2005). b. Subcortical regions damaged in patients with unilateral neglect include the caudate and putamen in the basal ganglia and the pulvinar nucleus in the thalamus.

1.4 Mechanisms behind unilateral neglect

Three main mechanisms have been hypothesized to account for the symptoms of neglect, namely deficits in attention, in representation (Karnath, Milner, & Vallar, 2002) and/or in motor-intention. The attentional account claims that patients with neglect may display unawareness of left side stimuli (Riddoch & Humphreys, 1983), ipsilesional attentional bias (Heilman & Watson, 1977; Kinsbourne, 1970), as well as difficulties in shifting attention from the ipsilesional to the contralesional side (Posner, Walker, Friedrich, & Rafal, 1984). In addition, the representation account argues that due to the deterioration of the stored representation of the left space, patients might have difficulties describing the left-sided details of imagined or recalled objects and scenes (Bisiach & Luzzatti, 1978; Denny-Brown & Banker, 1954). On the other hand, the motor-intentional account states that patients might be able to attend to stimuli in the contralesional side and yet show deficits in moving toward them (Coslett, Bowers, Fitzpatrick, Haws, & Heilman, 1990; Heilman et al., 1984; Watson, Miller, & Heilman, 1978). Throughout this thesis, such deficits in contralateral aiming movement are referred to as DMD. It should be noted that the three mechanisms described above are not necessarily mutually exclusive. Their coexistence might rather help to understand the complex nature of neglect.

1.5 Directional motor deficits associated with unilateral neglect and their assessment

Among the mechanisms proposed to explain UN, the deficits in contralateral aiming movement (also called "aiming" or motor-intentional bias) have attracted increasing interest from researchers over the last two decades. Having noticed that the majority of research had largely emphasized the importance of input or perceptual-attentional factors in neglect (Mattingley, Bradshaw, & Phillips, 1992; Mattingley & Driver, 1996), numerous studies aimed to explore whether impairments in initiating and/or executing movements in or toward the contralesional side of space might accompany or fully explain symptoms of neglect (Bisiach, Geminiani, Berti, & Rusconi, 1990; Coslett et al., 1990; Heilman, Bowers, Coslett, Whelan, & Watson, 1985; Husain, Mattingley, Rorden, Kennard, & Driver, 2000; Mattingley, Bradshaw, & Phillips, 1992; Na, Adair, Williamson, Schwartz, & Haws, 1998; Tegnér & Levander, 1991). Accordingly, different techniques were devised to specifically assess such impairments and differentiate them from those attributed to perceptual-attentional factors. Some of these techniques, known as opposition techniques, made use of mirror-viewing conditions (Tegnér & Levander, 1991), incongruent response devices (Bisiach et al., 1990; Halligan & Marshall, 1989), and inverted video recordings of hand movements (Coslett et al., 1990; Ghacibeh et al., 2007). By manipulating visual feedback, they attempted to uncouple the direction of the participants' hand movement from the location of the perceived visual target. However, these techniques were extensively criticized for entailing highly confusing and demanding cognitive tasks that could lead to erroneous interpretations. Alternatively, other techniques aiming at examining DMD in more natural settings, employed reaching tasks with variable starting positions (Husain et al., 2000; Mattingley et al., 1992; Mattingley, Husain, Rorden, Kennard, & Driver, 1998; Sapair, Kaplan, He, & Corbetta, 2007) as well as different adapted versions of the Landmark Task (Brighina et al., 2002; Harvey, Milner, & Roberts, 1995; Vossel et al., 2010). The latter task was introduced by Milner, Harvey, Roberts, & Forster., (1993) and Harvey et al., (1995) to assess whether the symptoms displayed by neglect-patients might derive mainly from perceptual or motor impairments. It consists of a series of pre-bisected lines which are successively presented to patients, whose task is to judge in different ways whether the lines are correctly bisected. Some studies instruct patients to answer manually or verbally which segment of the line is shorter and which one is larger (e.g. Vossel et al., 2010). By means of this instruction it is assessed whether the frequency with which patients opt for one or the other side suggests either an impairment in directing hand movements toward the contralateral side (compatible with a motor impairment), or a tendency to underestimate the left side while overestimating the right one (compatible with a perceptual impairment). Other studies have aimed to compare the amount of rightward biases when patients perform neglect tasks eliciting perceptual vs. motor responses (e.g. Striemer & Danckert, 2010; Striemer et al., 2016). These tasks include, on the one hand, landmark tasks requiring patients to verbally judge whether the bisection mark is centrally located, and on the other hand, line bisection tasks instructing patients to manually locate the center of the lines. A similar approach is adopted in the study presented in the second chapter of this thesis, where patients' performance is assessed by means of a verbal landmark task together with a manual landmark task comparable to a line bisection task. Furthermore, in order to get a broader picture of patients' symptoms, a series of cancellation tasks are included in the assessment. These tasks are commonly used in the clinical setting and allow to not only examining motor performance but also visual search performance. In these tasks patients are presented with a sheet consisting of random and structured verbal (e.g. letters and numbers) and non-verbal (e.g. lines and stars) stimuli and their instruction is to cross out the target stimuli as fast and accurately as possible.

1.5.1 Characterization and neuroanatomy of directional motor deficits

With the help of the techniques mentioned in the previous section, DMD have been described in more detail. For instance, a distinction between spatial and temporal deficits has been made, with directional hypokinesia (slowing in the initiation of contralateral movements) and directional bradykinesia (slowing in the execution of contralateral movements) linked to the former, and directional hypometria (insufficient amplitude or spatial extent of contralateral movements) linked to the latter (Loetscher, Nicholls, Brodtmann, Thomas, & Brugger, 2012; Mattingley et al., 1992). In addition, other DMD akin to the spatial category, such as motor perseveration (inability to disengage from stimuli in the ipsilesional side) and directional impersistence (inability to sustain a movement toward the contralateral side) have been defined.

Moreover, it has been established that depending on certain brain-lesion patterns, patients might present with DMD either in addition to perceptual-attentional deficits or independently. However, due to the varied techniques used to identify them, conflicting anatomical findings have been obtained. On the one hand, a number of studies have pointed to the frontal lobe (Bisiach et al., 1990; Li, Chen, Guo, Gerfen, & Svoboda, 2015; Tegnér & Levander, 1991) and the basal ganglia (Sapir et al., 2007; Vossel et al., 2010) as the most commonly injured regions in patients with DMD. This more anterior and traditional localization perspective has been challenged by another view claiming that the exclusive damage to the IPL might cause a specific impairment in the planning and initiation of leftward movements toward left-sided targets (Husain et al., 2000; Mattingley et al., 1998).

1.5.2 Transcranial Magnetic Stimulation in the study of directional motor deficits

In view of the lack of consensus regarding the participation of anterior and posterior brain regions in DMD, two studies examined the possibility of inducing comparable deficits (DMD-like) in healthy subjects by applying TMS over frontal and parietal cortices (Brighina et al., 2002; Ghacibeh et al., 2007). However, their findings did not seem to agree with each other. Whereas the study by Ghacibeh et al., (2007) confirmed the participation of frontal areas in DMD, Brighina et al., (2002) indicated a relation between frontal areas and perceptual-attentional deficits, suggesting as an alternative that DMD are more likely to occur following subcortical damage. Moreover, none of them found an association between parietal regions and DMD. Contrary to this evidence, recent studies using single-pulse and paired-pulse TMS (Davare, Zénon, Desmurget, & Olivier, 2015; Koch, Fernandez, Olmo, Cheeran, & Schippling, 2008) have supported the idea that the IPL does actually participate in the planning and direction encoding of movements performed toward the contralateral (left) space. Although these studies were not originally conducted within the context of UN, their findings have somewhat contributed to elucidate the participation of IPL in DMD.

It is important to note that the application of TMS offers several advantages over other neuroscientific methods, such as neuroimaging and lesion-symptom mapping. In comparison to neuroimaging methods (e.g. fMRI, PET), which indicate correlations between behaviors and patterns of brain activity, TMS goes one-step further offering the possibility to explore causal relationships between them. By inducing a transient disruption or a so-called “virtual lesion” in a roughly delimited region in the brain, this technique examines whether the function of such a region is essential for the performance of a given task. If performance is impaired or delayed, it can be inferred that the stimulated area is in fact causally involved in the task. Furthermore, unlike lesion-symptom mapping, TMS allows the study of deficits rarely observed in neurological patients, enables a higher degree of anatomical specificity, and eliminates potential confounding effects attributed to functional reorganizational or compensatory processes. Taking into account such advantages, a TMS approach is used in the project presented in the first chapter.

1.6 Prism adaptation and its therapeutic value in the rehabilitation of unilateral neglect

In brief, PA is a phenomenon in which the active exposure to rightward displacing prismatic glasses (10 to 12 degrees) induces a shift in the perceived location of an object in the opposite direction of the optical displacement. Such an active exposure involves the continuous execution of pointing movements toward visual targets while wearing the glasses. During the first movement trials, subjects exposed to PA miss the target in the direction of the optical displacement (Figure 2a; initial error). However, after a series of trials visual feedback of the overshoot leads to motor correction in the opposite direction of the displacement (Figure 2b; error reduction). The PA phenomenon is experienced after the glasses have been removed and the exposed subjects try to perform reaching or pointing movements with the adapted hand. As a result of the shift in perception, movements become less accurate and subjects miss the target in the opposite direction of the displacement (compensatory or negative after-effect) (Figure 2c). The extent of the observed after-effect can be quantified by means of different parameters reflecting the amount of realignment in visual and/or proprioceptive spatial maps, namely, the proprioceptive shift, the visual shift, and the total shift (Jacquin-Courtois et al., 2013; Newport & Schenk, 2012). The first two parameters are generally assessed by comparing straight-ahead judgements made by patients immediately before and after the adaptation procedure, yet following different methods. When assessing the proprioceptive shift, patients perform pointing movements in the straight-ahead direction with their index finger either blindfolded or in the darkness. To assess the visual shift, on the other hand, patients are asked to interrupt the movement of a visual target moving laterally as soon as they judge that the target has reached a straight-ahead position. As for the assessment of the total shift, patients carry out a sequence of pointing movements in the direction of a visual target without seeing their hand (Rode et al., 2015). It should be noted that among all three parameters, the proprioceptive shift has been shown to provide a more reliable measure closely related to the pathological rightward biases in the subjective straight ahead, frequently exhibited by patients (Rode et al., 2015; Weiner, Hallett, & Funkenstein, 1983). Based on this evidence, this parameter is employed in the study presented in the second chapter of this thesis to quantify the magnitude of the after-effect displayed by a group of neglect patients.

When patients with neglect are exposed to PA their pathological rightward biases are often reduced and the judgement of their subjective midline approximates the true center. Two main mechanisms are thought to be involved in PA, namely the strategic error correction and the spatial realignment (Newport & Schenk, 2012). The former is characterized by the rapid adjustment of the movements so that the initial overshoot errors can be prevented. This is done by deliberately reaching slightly in the opposite direction of the target. The spatial realignment refers to a more unconscious mechanism by which the visual and proprioceptive coordinate systems are realigned.

PA is included among the group of interventions relying mostly on bottom-up mechanisms (Adair & Barrett, 2008; Rossetti et al., 2015). In contrast to other interventions (e.g. visual scanning training, cueing, and sustained attention training) requiring patients to maintain awareness of their left-sided deficits and actively learn a cognitive strategy to compensate for them (top-down approach), PA has a more passive character and requires less active participation of patients. This is explained by PA's dependency on low-level sensory-motor reorganizations thought to circumvent patient's impairments in awareness and intentional control. In fact, it has been suggested that conscious, strategic efforts aimed at changing movement direction might reduce adaptation effects (Adair & Barrett, 2008; Rossetti et al., 2015).

Since the pioneer study by Rossetti et al., (1998), which indicated an improvement in patients' neuropsychological performance following one session of PA, numerous studies have reported beneficial effects of this intervention on varied aspects of UN. Some of them indicated PA-related benefits in visuo-spatial tests traditionally used to assess UN symptoms, such as cancellation tasks, line bisection, figure copying and drawing, picture scanning, clock drawing and reading tasks (Farne, Rossetti, Toniolo, & Ladavas, 2002; Frassinetti, Angeli, Meneghello, Avanzi, & Làdavas, 2002). Other studies aiming at using more ecologically oriented tasks evidenced beneficial effects of PA on functional measures related to daily life activities. Some of the assessment tools used by them included questionnaires such as the Barthel index (Hideki, Toshiaki, Itou, Sampei, & Kaori, 2010), the Functional Independent Measure (FIM) (Mizuno et al., 2011), the Catherine Bergego Scale (CBS) (Chen et al., 2014) as well as wheel-chair driving activities (Jacquin-Courtois, Rode, Pisella, Boisson, & Rossetti, 2008). In opposition to the idea that the effects of PA might expand to all aspects of neglect, including sensory, motor and cognitive ones, a series of recent studies have pointed out that such effects might not be the same for visuo-motor and perceptual-attentional aspects of the disorder. More specifically they have suggested that whereas visuo-motor or motor-intentional aspects might be particularly prone to PA's influence, perceptual-attentional aspects might remain unchanged.

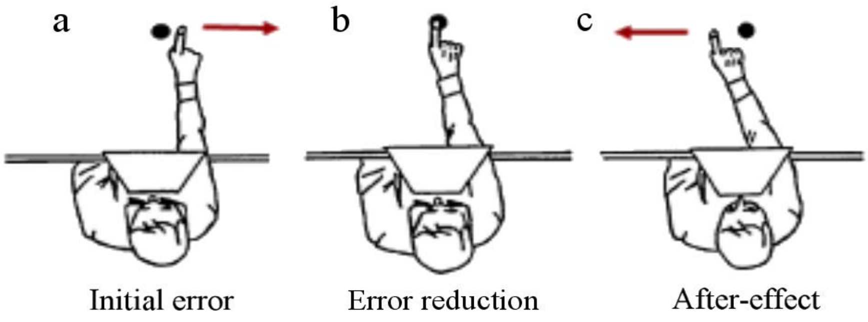

Figure 2. Illustration of the PA phenomenon. a. At the start of the adaptation process subjects miss the target in the direction of the displacement induced by the goggles (initial error). b. After a series of movements, visual feedback of the overshoot prompts a motor correction in the opposite direction of the displacement (error reduction). c. After removing the goggles subjects miss the target in the opposite direction of the displacement (after-effect) (adapted from Jacquin-Courtois et al., 2013).

1.6.1 Directional motor deficits and their particular relation to prism adaptation

The assessment of DMD has become increasingly important to explain the effects of PA in the rehabilitation of neglect. A series of studies in patients and healthy subjects have suggested that motor biases might be particularly ameliorated after sessions of PA (Barrett, Goedert, & Basso, 2012; Fortis, Goedert, et al., 2011; Goedert, Chen, Boston, Foundas, & Barrett, 2013; Striemer & Danckert, 2010). Likewise, it has been shown that such an intervention might exert a beneficial influence in tasks that require motor responses rather than in those requiring mainly a perceptual judgment (Striemer & Danckert, 2010; Striemer et al., 2016). More specifically, PA has been suggested to selectively improve patient's performance in the line bisection task, but not in perceptual versions of the landmark task. Altogether, these findings are especially relevant when trying to understand that some neglect patients might either respond to a lesser extent or not respond at all to PA. Thus, there is the possibility that patients' responsiveness to this intervention depends, among other factors, on whether their symptoms include DMD. Nevertheless, in line with the studies described above there is opposing evidence that PA might not only improve motor functions but also mental imagery and visual search performance (Gilles Rode, Rossetti, Li, & Boisson, 1998; Saevarsson, Kristjánsson, Hildebrandt, & Halsband, 2009; Vangkilde & Habekost, 2010). In light of these indications, it has been contemplated that brain lesion patterns and possibly further behavioral factors might also be important aspects to consider when assessing the potential effectiveness of PA.

1.6.2 Neuroanatomical and behavioral factors associated with prism adaptation's effectiveness

Some studies have aimed at exploring potential neuroanatomical and behavioral factors associated with a higher chance of PA' success. However, similar to the controversies surrounding the neuroanatomy of DMD and UN in general, contrasting findings have also been reported. As to the neuroanatomical aspects associated with PA's efficacy, the intactness of different brain areas including cerebellar (Luauté et al., 2006), occipital (Serino, Angeli, Frassinetti, & Làdavas, 2006), parietal (Luauté et al., 2006; Sarri et al., 2008; Striemer & Danckert, 2010), temporal (Chen et al., 2014), and frontal (Sarri et al., 2008) cortices has been indicated. As to the participation of frontal regions, two voxel-based lesion-symptom mapping (VLSM) studies have interestingly suggested that frontal damage might rather facilitate patients' response to PA (Chen et al., 2014; Gossmann, Kastrup, Kerkhoff, López-Herrero, & Hildebrandt, 2013). It should be noted that, among the aforementioned studies, only three (Chen et al., 2014; Gossmann et al., 2013; Sarri et al., 2008) employed lesion-symptom mapping analysis (Rorden, Karnath, & Bonilha, 2007). Considering the importance of further examining the neuroanatomical bases of the improvement associated with PA, a lesion-symptom mapping approach is adopted in the study presented in the second chapter of this thesis.

Concerning the behavioral aspects associated with PA, besides the aforementioned role of DMD, it has been suggested that the extent of the after-effect displayed by patients in the first session might be a crucial predictor for treatment outcome. Some studies have actually reported a positive relation between the magnitude of the after-effect and the amount of long-term improvement in neuropsychological tasks (Farne et al., 2002; Sarri et al., 2008). However, other studies have described cases of patients showing improvements despite not having experienced any after-effect and vice versa (Pisella, Rode, Farné, Boisson, & Rossetti, 2002). It should be underlined that the general term after-effect has sometimes been indifferently used to refer to the total or the proprioceptive after-effect. This misuse has led to the misconception that the after-effect is essentially associated with the improvement in neglect symptoms.

1.7 Aims of the thesis

The overarching goal of this thesis was to provide further insights into some controversies surrounding the neuroanatomical underpinnings and rehabilitation of the DMD associated with UN. Broadening our knowledge of these aspects is of great importance not only to better appreciate the participation of right brain areas in contralateral aiming movement but also to design more effective and individually adapted interventions for the treatment of UN. In line with these motivations, Chapter 2 of this thesis presents an opinion article remarking the need to systematically assess DMD and account for their contribution to neglect rehabilitation.

This thesis had two main aims. The first one was to shed some light on the debated role of frontal vs. parietal lesions in the occurrence of DMD. To that end, in the first project of this thesis (Chapter 3) repetitive pulses of transcranial magnetic stimulation (TMS) were delivered to right angular and middle frontal gyri while a group of healthy participants performed an auditory choice task involving pointing movements toward two laterally located targets. Thereby, it was examined whether movement difficulties comparable to DMD might be induced by either stimulation and inferences were drawn about the involvement of the stimulated areas in the planning and execution of contralateral aiming movements.

Furthermore, this thesis aimed to advance our understanding of controversial neuroanatomical and behavioral factors associated with the efficacy of PA. Correspondingly, in the second project (Chapter 4) a lesion-symptom mapping analysis was conducted in a group of patients with left unilateral neglect who underwent a three-session protocol of prism adaptation, including two sessions of intervention combined with neuropsychological assessment and one follow up session of assessment only. Among the behavioral factors, the relationship between the magnitude of the initial proprioceptive after-effect and the potential improvement in neuropsychological performance across sessions was examined. Furthermore, considering the suggested link between DMD and the therapeutic outcomes of PA, it was explored whether any potential improvement might be particularly evident in neuropsychological tasks requiring motor responses. As to the neuroanatomical factors, this project aimed to identify patterns of brain lesion associated with a higher vs. a lower improvement in neuropsychological performance.

2 Neglected premotor neglect

This chapter includes an opinion article entitled "Neglected premotor neglect". This article questions the tendency to consider directional motor deficits as being unrelated to unilateral neglect, remarking instead the need to systematically assess them and account for their contribution to neglect rehabilitation. This opinion article was published in Frontiers in Human Neuroscience in 2014.

Contributions:

Authors: *Styrmir Saevarsson; Simone Eger; Maria Gutierrez-Herrera.*

The author of this thesis is a co-author of the opinion article; S.S. formulated the topic and focus of the article; S.S., M.G.-H and S.E wrote the article.

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Neglected premotor neglect

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Unilateral neglect, or neglect for short, is commonly described as the failure to respond and attend to stimuli presented on the contralesional side. It cannot be explained by primary motor and sensory impairment (Heilman et al., 1987), and is usually caused by a stroke. Although neglect patients often recover spontaneously within several weeks, they demonstrate poorer amelioration and require longer hospitalizations following a stroke compared to stroke patients without the affliction (e.g., Buxbaum et al., 2004; Gillen et al., 2005). Many different subforms of neglect have been specified to date (e.g., Saevarsson et al., 2011). One of these, premotor neglect (PMN; also known as intentional motor neglect, directional action neglect, etc.; see Saevarsson, 2013a) denotes an intentional, voluntary, and directional (e.g. eye, hand, and head) motor bias from the ipsilesional side to an object in the contralesional side of space (Watson et al., 1978; Halligan and Marshall, 1989; Bisiach et al., 1990; Goodale et al., 1990; Heilman et al., 2008; Saevarsson, 2013a). For instance, patients may fail to reach an apple on their left side with their right hand (i.e., directional akinesia; Heilman et al., 1987) although they may be visually aware of the object. The foundation of PMN diagnosis is based on various studies that indicate performance improvement or decline when patients perform tasks that require directional movements under different visual conditions (see Saevarsson, 2013a for discussion). PMN is often seen alongside other neglect forms (in approximately 45% of cases), although exact incidence has not been specified (Saevarsson, 2013a). Unfortunately, many neglect reviews and empirical studies ignore PMN altogether (e.g., Saevarsson et al., 2008; Karnath, 2014), or report it merely as an unimportant accompaniment and not specific to neglect (e.g., Himmelbach and Karnath, 2003; Rossit et al., 2009a; Striemer and Danckert, 2013). For example, Himmelbach et al. (2007, p. 1980) claim that PMN is not a "consequence of spatial neglect but rather indicate[s] a phenomenon occurring in some of these patients as well as in other stroke patients (without neglect), i.e., a phenomenon occurring with (so far not further identified) brain damage." In line with this view, the number of studies on PMN have decreased considerably since the 1990s (Saevarsson, 2013a). Conversely, many authors argue for the importance of PMN (e.g., Mattingley and Driver, 1997; Konczak and Karnath, 1998; Vossel et al., 2010; Saevarsson, 2013b) although non-neglect-based terms such as directional hypokinesia are often used. For instance, the most commonly applied neglect definition of Heilman et al. (1987) refers to PMN when describing the affliction. Controversially, current mainstream literature does not reject this description despite the fact that some authors seem to prefer "spatial" or "hemispatial" neglect as a synonym, although representational neglect is non-spatial in nature. The nature of PMN is poorly understood and may hold the key to advanced neglect assessment and rehabilitation (Punt and Riddoch, 2006; Saevarsson, 2013a), thus we argue for the existence and importance of PMN with regard to various clinical, neuroanatomical, and methodological issues.

Previous studies questioning the importance of PMN suffer from significant methodological limitations. This is partially due to difficulties in differentiating between similar PMN and visual neglect symptoms (see Saevarsson, 2013a for discussion). Performance on standard and PMN tests can be interpreted as indicating visual neglect (i.e., failure to notice items on the left side; e.g., Làdavas et al., 1993) and PMN (see Mattingley and Driver, 1997; Saevarsson, 2013a). Rossit et al. (2009a,b) revealed that stroke patients with and without neglect showed similar impaired reaches to the left side. They concluded that the directional reaching deficits were non-neglect-specific (see also Himmelbach and Karnath, 2003; see Kim et al., 2013 for similar findings and methods but different interpretation of PMN). Noticeably, they report only the group results with high standard errors on their reaching tasks. It is therefore uncertain how the patients performed individually. In other words, it is not clear what percentage of the groups demonstrated reaching deficits to the contralesional side. It is important in this context that not all patients indicate PMN symptoms; therefore, it is uncertain whether a group of patients is representative of PMN. In other words, by diluting the group with patients who do not suffer from PMN, it is not likely to reveal any difference in PMN testing between two groups of right-brain damaged patients that do and do not have neglect (Rorden et al., 2007). This would be evident in a group of neglect patients in which none or only few suffered from PMN. Similarly, Himmelbach and Karnath (2003) criticize various studies (e.g., Husain et al., 2000) that compare reaching deficits in right-brain damaged neglect patients to healthy subjects. To test this point empirically, it would be questionable, for instance, to evaluate a group of patients with neglect in order to explore motor neglect since only a proportion of patients with neglect suffer from motor neglect (Saevarsson, 2013a). Or in Brewer's (1994, p. 119) words: "It is a mistake, in my view, to try to unify the wide variety of phenomena classified as manifestations of "neglect," by appeal to a single diagnostic or explanatory model of the neglect deficit." Moreover, Rossit et al. (2009b,a) used mainly the Behavioral Inattention Test (BIT; Wilson et al., 1987) to diagnose neglect in right-hemisphere-injured patients. It is debatable whether to divide participants into neglect and non-neglect subgroups when using the BIT as it does not provide an adequate assessment unless used alongside additional diagnostic resources that are not sensitive to personal and extrapersonal neglect; in addition, the BIT cannot distinguish between the motor and perceptive components of neglect (Plummer et al., 2003). No cut-off scores are given for the BIT and no clear evidence exists for its validity (Cermak and Hausser, 1989). Additionally, therapists sometimes complain that patients perform well on the BIT although their neglect manifests itself clearly in more stressful circumstances in daily life (e.g., Hjaltason and Saevarsson, 2007).

Neuroanatomical evidence against the existence of PMN is infirm and contradictory. Rossit et al. (2009a,b) highlight nodes in the basal ganglia, occipito-parietal cortex, and frontal lobe as being responsible for directional reaching deficits in stroke patients, and claim that these areas are not associated with neglect *per se*, citing the neuroanatomical findings of Karnath et al. (2001, 2004) and Mort et al. (2003). Furthermore, Rossit et al. indicate that damage in the inferior parietal cortex involved in reaching and awareness deficits to the left side was also responsible for directional reaching deficits without neglect. Similarly, Himmelbach and Karnath (2003) hypothesize that the posterior parietal and superior temporal cortex are responsible for directional reaching, and the inferior parietal lobe and superior temporal cortex produce spatial neglect and directional reaching deficits. Many areas of the brain, such as the inferior parietal cortex, temporo-parietal junction (e.g., Mort et al., 2003), superior temporal cortex (Karnath et al., 2004), frontal lobe (Husain and Kennard, 1996; Ghacibeh et al., 2007), and basal ganglia (Karnath et al., 2002; Vossel et al., 2010) are widely believed to be involved in neglect. Therefore, Rossit and Himmelbach et al.'s perspectives differ significantly from other neuroanatomical studies. In other words, by indicating a common neuroanatomical mechanism (e.g. Mattingley et al., 1998; Muggleton et al., 2006), Rossit and others may explain isolated reaching deficits to the left side in neglect. Moreover, Karnath et al. (2001, 2004) and Mort et al. (2003) did not control for directional motor deficits in their studies, therefore making a comparison to the studies of Rossit and Himmelbach and others impossible. Phrased differently, lesion-symptom mapping of two different groups requires symptoms that differ in order to be able to map the area of interest (Rorden et al., 2007). Furthermore, Rossit et al.'s (2009a,b) and Himmelbach and Karnath's (2003) sample sizes were only 11, 11, and six neglect patients, respectively, which is likely too small for a meaningful lesion-symptom study. Statistical power is a major concern due to the location distribution of brain lesions (Kimberg et al., 2007). Crucially, there is currently no final agreement on the critical neuroanatomical bases of neglect and PMN due to various methodological assessment issues (see Danckert and Ferber, 2006; Saevarsson, 2013a,b; Saevarsson and Kristjánsson, 2013).

To account for this discrepancy, it is suggested that directional motor deficits observed in right-brain injured patients "without neglect" (who may not suffer from peripersonal visual neglect) indicate PMN that is not coupled with peripersonal visual neglect, or PMN coupled with unspecified visual neglect form. This interpretation is likely since neglect patients commonly indicate double dissociations with respect to visual neglect. For example, Butler et al. (2004) related severity of peripersonal visual neglect to dorsal stream injury and extrapersonal visual neglect to ventral stream damage. Moreover, isolated forms of PMN in right-hemisphere injured patients may be quite common (see Saevarsson and Kristjánsson, 2013 on no neglect improvement following prism adaptation). Indeed, the literature indicates isolated cases of the affliction where only one modality, such as motor or conceptual, is affected (e.g., Laplane and Degos, 1983; Ortigue et al., 2001). Therefore, Himmelbach and Rossit et al. tested right-hemisphere injured patients that may have suffered from an isolated form of PMN and other forms of non-diagnosed neglect. Furthermore, several authors claim that different neuroanatomical mechanisms may explain isolated forms of neglect within the syndrome (e.g., Chechlacz et al., 2012). Coulthard et al. (2006, 2007) argue against the idea that impairments found only in neglect are the sole indication of what the syndrome is. Instead, they assert that neglect is a combination of a group of mental deficits such as impaired spatial memory and directional motor deficits. They explain that PMN can consist of less efficient contralesional reaches and target location on one side, but not to both directions. However, whether and how PMN belongs to the neglect syndrome, should be a central issue when explaining neglect as it affects its assessment and therapy (Saevarsson, 2013b). Indeed, non-sensory factors of movement may be better indicators of poor clinical outcomes than sensory ones (Punt and Riddoch, 2006). PMN and visual feedback are believed to be predictors of successful prism adaptation therapy for neglect (Saevarsson et al., 2009; Striemer and Danckert, 2010a,b; Saevarsson, 2013b; Saevarsson and Kristjánsson, 2013). For instance, Goedert et al. (2014) found bigger improvements on various neglect tests following two weeks of prism adaptation therapy by PMN patients compared to patients suffering from visual neglect without PMN. Similarly, practicing limb movements (Robertson et al., 1992; Pitteri et al., 2013) and increasing contralesional eye movements with prism adaptation intervention improves neglect (Serino et al., 2006). It is also proposed that unspecified frontal and parietal areas play a crucial role in PMN, even if its exact neuroanatomical mechanism is largely not understood. Saevarsson (2013a) reviews 43 studies that apply various assessment approaches and concludes that frontal and parietal structures are most commonly injured in PMN. For instance, Vossel et al. (2010) measured a visual and response bias in neglect with the "turned" manual Landmark task. They found that a visual bias in neglect is caused by frontal, parietal, and occipital injury, while caudate nucleus and putamen were associated with PMN. Mattingley et al. (1998) used a left-right response button task to explore these same components. They show that brain lesions in the inferior parietal lobe—not frontal cortex—explain PMN symptoms and suggest that the inferior parietal lobe operates as a sensorimotor interface. In addition, ignorance of PMN aspects of neglect assessment and the methodological limitations of BIT with respect to neuroanatomical underpinnings call our current understanding of neglect into question (Plummer et al., 2003; Saevarsson, 2013a). Lastly, we call for PMN to be systematically addressed (see Mattingley and Driver, 1997; Saevarsson, 2013a for a discussion and suggestions of PMN assessment) in *every* study on perceptual neglect that requires directional movements because of difficulties in differentiating between the clinical effects of these two subgroups of PMN and visual neglect. One can claim that the critiques of Rossit et al. (2009a) and others are imperfect and that the contralesional directional action components of neglect should remain a part of the standard definition and assessment focus (Saevarsson, 2013a).

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3 Repetitive TMS in right sensorimotor areas affects the selection and completion of contralateral movements

The current chapter includes a research article entitled “Repetitive TMS in right sensorimotor areas affects the selection and completion of contralateral movements”. This article suggests that right angular and middle frontal gyri contribute to different aspects of contralateral aiming movement. Whereas the former is involved in the initial selection of contralateral movements, the latter is responsible for maintaining the goal and committing to the decision to move in the contralateral direction. The manuscript was published in Cortex in 2017.

Contributions:

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The author of this thesis shares the first authorship of the manuscript with Styrmir Saevarsson; S.S. conceived and designed the study, with the help of J.H and W.S; M.G.-H conducted the MRI acquisition and pre-processed the images under the supervision of T.H and W.S; M.G.-H. implemented and performed the experiment; M.G.-H conducted data analyses; M.G.-H, W.S and S.S wrote the manuscript; J.H. provided critical feedback on the manuscript, which was further commented by T.H.

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Research Report

Repetitive TMS in right sensorimotor areas affects the selection and completion of contralateral movements

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ABSTRACT

Although the existence of directional motor deficits (DMD) associated with movement planning and/or execution seems to be widely recognized, neglect and single cell studies examining their neuroanatomical foundation have produced contradictory and inconclusive findings. The present study assessed the occurrence of DMD following the application of repetitive transcranial magnetic stimulation (rTMS) over two regions, as commonly reported in the neglect literature, namely the right middle frontal gyrus (rMFG) and the right angular gyrus (rAG). Fourteen healthy subjects underwent rTMS while performing an auditory choice task, involving pointing toward two laterally located targets, under internally (i.e., pointing side freely selected) and externally guided conditions (i.e., pointing side guided by spatial auditory cues). In order to examine whether subjects compensated for induced deficits with the help of vision, visual feedback was occluded at movement onset in half of the trials. rTMS applied to the rAG significantly increased reaction times (RTs) for leftward internally-guided movements. In contrast, rTMS applied to the rMFG reduced the likelihood to complete leftward internally-guided movements under blindfolded conditions. These effects suggest that DMD might involve cognitive processes contributing to the different stages of motor control, such as movement selection and goal maintenance.

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1. Introduction

Over the last two decades a number of neuropsychological studies (Husain, Mattingley, Rorden, Kennard, & Driver, 2000; Sapir, Kaplan, He, & Corbetta, 2007; Vossel, Eschenbeck, Weiss, & Fink, 2010) have indicated that, in addition to the perceptual difficulties traditionally associated with the neglect syndrome, patients may exhibit motor deficits hindering the planning and/or execution of eye (Behrmann, Ghiselli-Crippa, & Dimatteo, 2002) or hand movements toward the contralesional space (Heilman, Bowers, Coslett, Whelan, & Watson, 1985; Mattingley, Bradshaw, & Phillips, 1992; Saevarsson & Kristjánsson, 2015). Some deficits affect temporal performance and include delayed initiation (directional hypokinesia; Heilman et al., 1985; Mattingley et al., 1992; Meador, Watson, Bowers, & Heilman, 1986) and slow execution of movement (directional bradykinesia; Karnath, Dick, & Konczak, 1997; Mattingley, Bradshaw, Bradshaw, & Nettleton, 1994). A second group of motor deficits relates to spatial performance and is indicated by the inability to make movements in the contralesional direction (spatial exploration reduction; Tegnér & Levander, 1991) as well as by the reduced amplitude of contralesional movements (directional hypometria; Bisiach, Geminiani, Berti, & Rusconi, 1990; Mattingley, Phillips, & Bradshaw, 1994; Meador et al., 1986). In line with neuropsychological studies, some lesion studies in monkeys (Deuel & Farrar, 1993; Faugier-Grimaud, Frenois, & Peronnet, 1985) have described the presence of comparable deficits to those listed above.

Although the existence of these deficits is seemingly widely recognized, the investigation of their neuroanatomical foundation has produced contradictory and inconclusive findings (Saevarsson, 2013; Saevarsson, Eger, & Gutierrez-Herrera, 2014), with common lesion sites ranging from right posterior parietal (Battaglia-Mayer, Mascaro, Brunamonti, & Caminiti, 2005; Husain et al., 2000; Koch, Fernandez, Olmo, Cheeran, & Schippling, 2008) to subcortical (Sapir et al., 2007; Vossel et al., 2010) and right frontal areas (Bisiach et al., 1990; Ghacibeh, Shenker, Winter, Triggs, & Heilman, 2007; Li, Chen, Guo, Gerfen, & Svoboda, 2015; Tegnér & Levander, 1991). It is worth noting that, although frontal and subcortical areas occupy a prominent place in directional motor deficits (DMD) literature, the inferior parietal lobe (IPL), and more specifically the angular gyrus (AG), seems to play an important role as well, by participating in the earliest stages of planning movement to the contralateral space (Husain et al., 2000; Koch et al., 2008; Sapir et al., 2007).

In addition to lesion mapping procedures in neglect patients, an alternative and more anatomically selective method to study the brain areas involved in DMD is transcranial magnetic stimulation (TMS). To date, only two repetitive transcranial magnetic stimulation (rTMS) studies have addressed the neuroanatomical underpinnings of DMD (Brighina et al., 2002; Ghacibeh et al., 2007). The first examined whether rTMS applied to right parietal and right frontal areas during the execution of a verbal Landmark task could induce perceptual or motor neglect deficits (Brighina et al., 2002). It was found that none of the stimulation conditions resulted in motor deficits but instead subjects showed perceptual deficits under both conditions. The second study tested the hypothesis that rTMS applied to right parietal and frontal areas would induce perceptual and motor deficits, respectively (Ghacibeh et al., 2007). The stimulation was delivered while subjects performed a line bisection task in which they could see a display of their videotaped hand either in a realistic or a mirror reversed orientation. When the right middle frontal gyrus (rMFG) was stimulated, subjects demonstrated rightward biases during both orientations, which was interpreted as an indicator of DMD.

Taking into account the contrasting evidence regarding the participation of frontal and parietal areas in DMD, the present study used rTMS in combination with kinematic measures to more precisely explore the role of two regions commonly reported in the neglect literature, namely the right angular gyrus (rAG) and the rMFG, in the planning and execution of contralateral aiming movements. We define movement planning as the preparation of the appropriate motor commands conducive to achieving a goal, whereas movement execution refers to the implementation and online monitoring of such commands (cf. Xivry, Legrain, & Lefèvre, 2016). Accordingly, we examined whether the application of rTMS over the two target areas could induce difficulties comparable to DMD in healthy subjects. To this aim we employed an auditory choice task involving lateral pointing movements similar to the one used by Koch et al. (2008) in their first experiment, but modified to accentuate the intentional aspect of movement. Given that DMD are predominantly considered to be specific to movement planning and that various neglect studies have emphasized their intentional nature, we used a task condition requiring subjects to internally (i.e., voluntarily) choose the direction of the movement. Further, such internal condition was contrasted with an external one, in which a tone indicated the pointing direction. Furthermore, since there is evidence that directional movement aspects rely on functions of the ipsilateral hemisphere (Busan et al., 2009; Farnè et al., 2003), the task was executed with the right hand. Additionally, in order to assess the contribution of vision to the online control of aiming movements, visual feedback was removed at movement onset in half of the trials. In these trials participants were prevented from using vision to compensate for any induced impairment.

Contrary to previous rTMS studies, the present study used kinematic measures together with a simple movement task, allowing a more detailed characterization of the roles played by the two examined areas in contralateral aiming movement. This is particularly relevant considering that the only studies using kinematic measures to assess DMD have so far been performed on patients with extensive brain lesions (Karnath et al., 1997; Mattingley, Husain, Rorden, Kennard, & Driver, 1998; Sapir et al., 2007). Based on the indications that frontal lesions might cause rightward motor biases and motor-intentional or "exploratory" deficits to the left hemispace (Chen, Goedert, Shah, Foundas, & Barrett, 2014; Ghacibeh et al., 2007; Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2010), we hypothesized that rTMS applied to the rMFG would cause a reduced frequency of leftward internally guided movements. In addition, because symptoms of directional bradykinesia have been frequently reported in patients with frontal damage, we expected rMFG stimulation to increase movement times (MTs) for leftward movements (Husain et al., 2000; Mattingley et al., 1992). As to the effects of parietal stimulation, we hypothesized that the transient disruption of rAG's function would result in prolonged reaction times (RTs) for leftward pointing movements. This hypothesis was motivated by evidence supporting rAG's participation in contralateral movement planning and initiation (Koch et al., 2008; Mattingley et al., 1998). Moreover, such presumed impairment in movement planning might be further reflected in a disproportional decrease in terminal pointing accuracy (TPA), particularly under conditions where visual feedback was removed at movement onset (Rossit et al., 2009; Striemer, Chouinard, & Goodale, 2011). Finally, considering the intentional nature attributed to DMD, we hypothesized that the potential impairments previously described would be more pronounced under internally guided conditions, which rely on self-initiation during motor planning.

2. Materials and methods

2.1. Participants

Seventeen right-handed healthy volunteers (nine women, eight men, mean age = 28.7, age range = 21–41 years) participated in this experiment. Handedness was determined based on a German version of the Edinburgh Handedness Inventory (Oldfield, 1971). All participants were carefully screened for TMS contraindications with the assistance of a collaborating physician. In accordance with the declaration of Helsinki, participants provided written informed consent after attending an informative session about the effects and potential risks of rTMS. The experimental protocol was approved by the Ethics Committee of the Medical Faculty of the Technical University of Munich (registration number: 5885/13).

Except for one participant who experienced repetitive stimulation as too painful and uncomfortable to continue with the experiment, all participants tolerated the rTMS protocol well and did not report any adverse effect. Two other subjects were excluded from the study since they showed systematic response patterns in the internally guided conditions during most of the stimulation conditions (see Data Analysis subsection for details). This led to a final sample of fourteen participants (eight women, six men, mean age = 29, age range = 23–41 years).

2.2. Procedure

Participants were comfortably seated on a padded chair in front of a height adjustable table (60 cm width/80 cm length) on which two targets (two lines 0.5 thick and 2.5 cm long intersecting at an angle of 90°) were located laterally (left and right) to a central start button (diameter 19 mm). The targets were drawn on the table, each at a 30 cm distance and at a 45-degree angle to the start button. The button was positioned 10 cm from the front edge of the table and aligned with the subject's sagittal midline (Fig. 1). Each trial started with the participant pressing and holding down the start button with the right index finger. Following a random delay of 6–9 sec, an auditory cue instructed the participant to reach out and point to either of the targets as quickly and accurately as possible, under the following two task conditions. During the internally guided (IG) condition, participants had to freely decide whether to point to the right or to the left target and execute the movement immediately after hearing a buzzing tone (100 Hz, 300 msec) presented bilaterally through in-ear headphones. In the externally guided (EG) condition, the direction of the pointing movement depended on the spatial location of the tone source: the presentation of a tone (600 Hz, 300 msec) from the right in-ear headphone should trigger a rightward pointing, with leftward pointing triggered by the presentation of the same tone from the left in-ear headphone. After completing the movement, the hand had to return to the start button and hold it down until the presentation of the next tone (Fig. 1A). In order to examine whether subjects compensated for induced deficits with the help of vision, they wore liquid crystal display (LCD) shutter glasses (PLATO, translucent Technologies, Inc., Toronto, Canada), which changed unpredictably from a clear to an opaque state upon the release of the start button (i.e., initiation of the pointing movement) in half of the trials. The opaque state prevented seeing the arm, hand and target for the entire duration of the movement. The glasses opened again when the participant pressed the start button after the movement had been executed (Fig. 1C). The two task conditions (IG *vs* EG) were combined with two visual feedback conditions (blindfolded *vs* sighted), resulting in four paired experimental conditions: internally guided – blinded (IB); internally guided – sighted (IS); externally guided – blinded (EB); and externally guided – sighted (ES).

Altogether, the experiment consisted of four blocks: two with effective rTMS applied to the rMFG and the rAG; one block with sham rTMS (coil oriented away from the head); and a control block without TMS stimulation (see below for details). Each paired condition (IB, IS, EB, and ES) was repeated twelve times per block, and the forty-eight resulting trials were presented in random order. None of the conditions was repeated more than three times in a row. Additionally, in order to obtain a comparable number of left and right directed movements during the externally guided conditions (ES and EB), half of the auditory cues were presented from the left in-ear headphone and the other half from the right one. During the internally guided conditions (IS and IB), participants were asked to distribute their responses randomly between both target directions and not to follow a fixed repetitive pattern. Prior to the experiment, they underwent 30 practice trials in order to familiarize themselves with the task.

2.2.1. Movement recording

With the purpose of analyzing hand movements, an infrared motion capture system was used to record the movement of a reflective marker attached to the tip of the right index finger (Qualisys, Göteborg, Sweden). Pointing movements were recorded at a sampling rate of 120 Hz using five Oqus cameras placed around the table. Movement recording started with the presentation of the cueing tone and went on for three seconds.

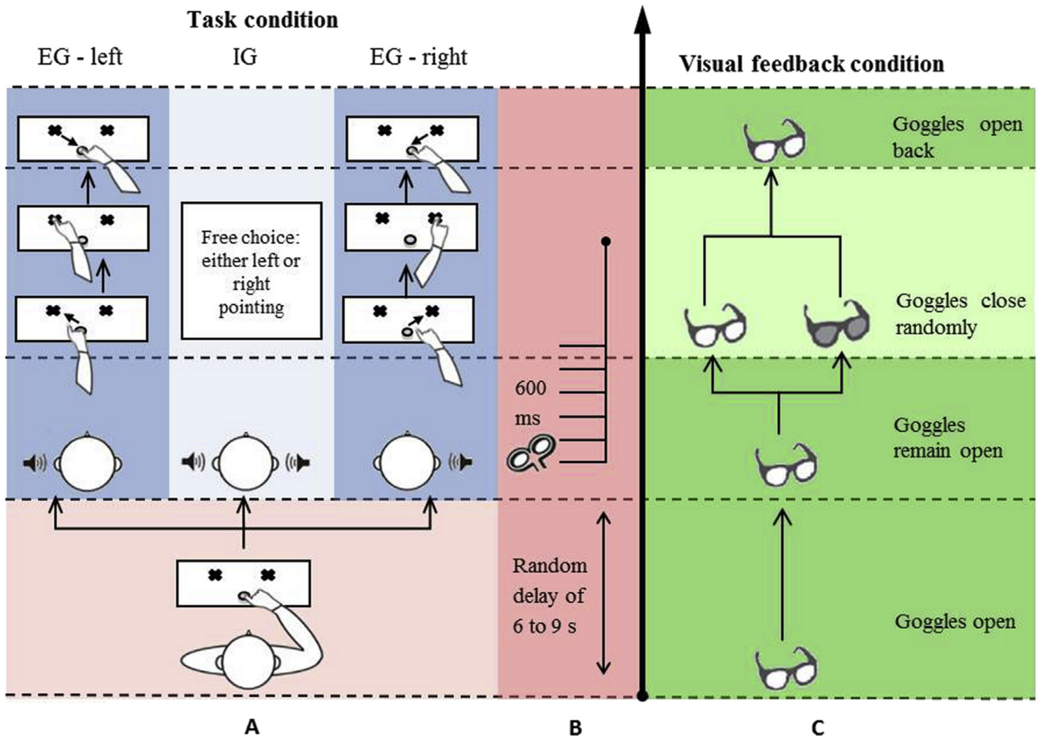

Fig. 1 — Schematic illustration of the experimental setup. (A) At trial onset, participants pressed and held down the central start button. Following the presentation of an auditory cue (randomly played 6–9 sec after the previous trial) signaling one of two possible task conditions (EG *vs* IG), they reached out and pointed to the left or right target with the right index finger. After completing the movement they pressed back the start button and waited until the next tone was presented. (B) Simultaneously with tone onset, rTMS trains of 600 msec (10 Hz, 6 pulses) were delivered in three stimulation conditions (rMFG rTMS, rAG rTMS, sham rTMS). An additional condition without TMS was also conducted. (C) In half of the trials the goggles worn by the participants closed randomly upon button release and opened again immediately after the button was pressed back.

2.2.2. *Neuronavigation and TMS protocol*

In order to monitor the TMS coil position in real-time, a frameless, ultrasound-based, stereotaxic neuronavigation system was used (BrainVoyager TMS Neuronavigator; BrainInnovation, Maastricht, The Netherlands). Prior to the TMS experiment, a 3D T1-weighted magnetization prepared rapid gradient echo (MPRage) scan (isotropic resolution 1 mm^3, TR/TE 9/4 msec) was obtained for each participant. Images were acquired on two 3-T magnetic resonance imaging (MRI) scanners (Ingenia, Philips Healthcare, The Netherlands; Magnetom Verio, Siemens, Germany).

Resting motor threshold (RMT) was determined with surface electromyography (EMG) using a descending adaptive staircase procedure. EMG activity was recorded from the left first dorsal interosseous muscle (FDI) with a PowerLab 8/35 amplifier (ADInstruments, Sidney, Australia). The RMT was defined as the minimum stimulus intensity capable of inducing motor evoked potentials (MEPs) greater than 50 μV peak-to-peak amplitude, in at least 5 out of 10 consecutive trials, upon single-pulse stimulation of the right primary motor cortex (M1). The optimal simulation hotspot was defined on the individual MRI scan as the center of the hand knob in the precentral gyrus, anterior to the central sulcus.

Brain targets were individually defined and localized using an MRI guided approach. The first target was defined as the region located on the dorsal portion of the rMFG adjacent to the precentral sulcus (average Talairach coordinates: $X = 37$, $Y = 6$, $Z = 55$). For the stimulation of this region the coil was placed tangentially to the scalp at 45° from the sagittal plane. The second target corresponded to the posterior region of the rAG neighboring the intraparietal sulcus (average Talairach coordinates: $X = 41$, $Y = -61$, $Z = 35$). This area was targeted with the coil positioned tangentially to the skull and the handle pointing downward and slightly medial (10°). In order to test for non-specific effects of rTMS, two control conditions were included. In the first one, the so called sham rTMS, the coil was positioned on the vertex with the front edge touching the scalp (i.e., the handle oriented vertically at 90° to the midline). In the second condition, no TMS was given in an attempt to control for the presence of facilitatory effects caused by the accompanying auditory and somatosensory stimulation.

During the experiment, rTMS was delivered in trains of 600 msec, at a frequency of 10 Hz and stimulation intensity 15% above the subject's individual motor threshold. rTMS was performed with a Power Mag 100 stimulator (MAG & MORE Company, Munich, Germany) attached to a double coil (figure-of-eight shaped). Stimulation trains started with the presentation of the tone and consisted of six single pulses (Fig. 1B). In accordance with the safety guidelines, intervals between stimulation trains varied randomly between six and nine seconds (Chen et al., 1997; Rossi et al., 2009; Wassermann, 1998). The software Presentation (Neurobehavioral Systems, Albany, CA, USA) was used to control the presentation of the auditory stimuli, open and close the shutter glasses, initiate movement recording, register responses, and trigger the TMS train pulses.

2.3. Data analysis

The 3D time-position data obtained by means of the motion capture system were filtered using a second order low-pass Butterworth filter with a cut-off frequency of 8 Hz (The MathWorks Inc., 2014). Four main variables were analyzed: two temporal measures including RTs (s) and MTs (s); and two spatial measures comprising TPA (mm) and the frequency of movements terminated at the left and at the right target during the IG condition. RTs, defined as the time between tone presentation and button release, were calculated using the event-timing information recorded via the Presentation software. MTs were designated as the time elapsed between leaving the start button and touching the target. They were calculated based on the first local minimum velocity reached at the moment of target contact. TPA was defined as the distance between the target and the tip of the index finger in the horizontal (x) and anterior-posterior (y) axes. Additionally, in order to dissociate the effects of the stimulation on the initial movement plan from any online corrective mechanisms induced by visual feedback (Kobak & Cardoso de Oliveira, 2014; Sainburg & Schaefer, 2004), we estimated movement direction at peak acceleration and computed two measures. First, the initial direction errors (IDEs), defined as the angular difference between the initial movement direction vector and the vector representing the straight path to the closest target; and second, the frequency of movements initiated toward the left and the right targets during the IG condition (frequency at the initial movement phase).

All trials whose RTs, MTs, TPA or IDEs fell outside the limit of two standard deviations from the mean of their conditions on a per-subject basis were excluded from the analysis (34 trials over all participants). Moreover, in order to make sure that participants had followed the instruction to distribute their IG responses randomly between both target directions, a randomness test, implemented in SPSS (Runs test; IBM SPSS Statistics, Version 22.0), was conducted on the movement sequence of each experimental block for each participant. Two participants who showed systematic response patterns in three and four stimulation conditions, respectively, were excluded from the analysis. The IG movement sequences displayed by these participants followed a fixed and systematic pattern in alternating between the target sides (e.g., making series of two or three consecutive IG movements towards each side repetitively).

For the statistical analysis, the mean values for RTs, MTs, TPA and IDEs were first averaged within task conditions and stimulation conditions for each participant and then analyzed using repeated-measures analyses of variance (ANOVAs). Four within-subject factors, namely, stimulation condition, task condition, movement direction and visual feedback, were included in the analysis of MTs and TPA. The same factors except for visual feedback were considered for RTs and IDEs, since until the moment of start-button release, full vision of the setup was provided under all conditions. For the analyses of the two frequency measures, at the initial phase and at the target, we employed a Generalized Estimating Equations (GEE) procedure with a Poisson regression model and a log link function. This approach is appropriate when analyzing frequency data collected in repeated-measures designs (Ballinger, 2004). This method was used to examine whether the number of movements terminated at the left or the right targets could be predicted by the main effects of the stimulation condition or the visual feedback, or by interactions between these factors. For the frequencies at the initial phase, a similar analysis but excluding the effect of visual feedback was performed. Given that the small sample size could affect the validity of the robust Wald test by inflating the probability of type I errors, the generalized score test was used to improve the performance of the sandwich estimator (Guo, Pan, Connett, Hannan, & French, 2005; Wan, Hua, & Xin M, 2012). In cases where the interaction between factors was statistically significant, post hoc analyses were performed using paired Student's *t*-tests with Bonferroni correction. For all conducted analyses, an alpha (α) value of .05 was used to define statistical significance.

3. Results

3.1. Reaction time (RT)

The 3-way ANOVA on RTs yielded a significant main effect of task condition, F (1, 13) = 38.23, $p < .001$, $\eta_p^2 = .75$. RTs of IG movements were significantly longer than those of EG ones. In addition, a significant three-way interaction effect was found between stimulation condition, task condition and movement direction, F (1.89, 24.64) = 3.99, $p = .033$, $\eta_p^2 = .23$ (Fig. 2). Paired *t*-tests, conducted to break down this interaction, indicated for IG movements significantly longer RTs in leftward ($M = .68$, $SD = .15$) compared to rightward movements ($M = .63$, $SD = .14$), only under conditions of rAG stimulation, t (13) = 3.28, $p = .006$. This difference remained significant after adjusting the alpha value with Bonferroni correction ($p = .048$). RTs of leftward IG movements were significantly longer under rAG stimulation ($M = .68$, $SD = .15$) than under frontal [($M = .61$, $SD = .14$), t (13) = −3.39, $p = .005$], control [($M = .63$, $SD = .12$), t (13) = −2.91, $p = .012$] and sham [($M = .64$, $SD = .11$), t (13) = 2.18, $p = .048$] stimulation conditions. Except for the sham contrast, which did not hold after Bonferroni correction, the contrasts involving frontal and control rTMS did remain significant after applying it (respectively $p = .015$ and $p = .036$). From these results, it can be noted that the prolongation of RTs observed in leftward movements was specific to rAG stimulation and occurred only when movement direction was freely selected. On the other hand, RTs of rightward movements were neither affected by stimulation condition, nor by task condition.

3.2. Movement time (MT)

The four-way ANOVA on MTs showed a significant main effect of movement direction, F (1, 13) = 39.61, $p < .001$ (Fig. 3), with

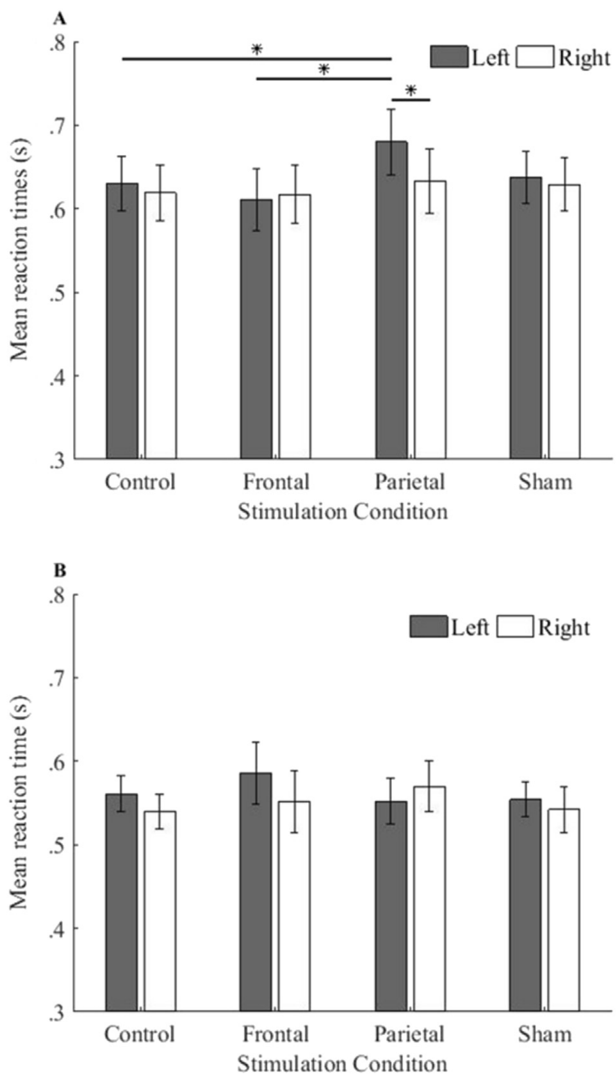

Fig. 2 – The effect of stimulation condition on RTs for (A) internally and (B) externally guided movements. The figure depicts the mean RTs in seconds as a function of stimulation condition and movement direction. The asterisks indicate significant differences between stimulation conditions. Error bars represent the standard error of the mean (SEM).

MTs of rightward movements being significantly shorter than MTs of leftward ones. Apart from movement direction, none of the other factors yielded significant main effects or interactions.

3.3. *Terminal pointing accuracy (TPA)*

The four-way ANOVA on TPA indicated a significant main effect of visual feedback, F (1, 13) = 21.57, $p < .001$ (Fig. 4). In line with previous literature on movement control, TPA of movements performed under blindfolded conditions was significantly reduced compared to that of movements performed in sighted conditions. Other than visual feedback, no other factors revealed significant main effects or interactions.

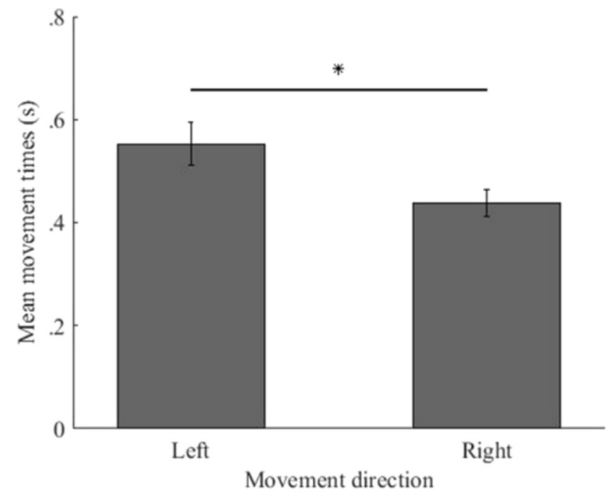

Fig. 3 – The effect of movement direction on MTs. The figure depicts the mean MTs in seconds as a function of movement direction. The asterisk indicates a significant difference between leftward and rightward movements. Error bars represent the SEM.

3.4. *Initial direction error (IDE)*

The three-way ANOVA on IDEs did not reveal any significant main effects or interactions (all $F < 1.303$, all $p > .287$).

3.5. *Frequency of movements initiated toward the left and the right targets under internal guidance*

As indicated by the GEE regression model, the effect of the stimulation did not explain the frequency of movements initiated toward the left (generalized score test $\chi^2 = 2.20$, $p = .531$) or the right (generalized score test $\chi^2 = 3.42$, $p = .331$) target under internal guidance.

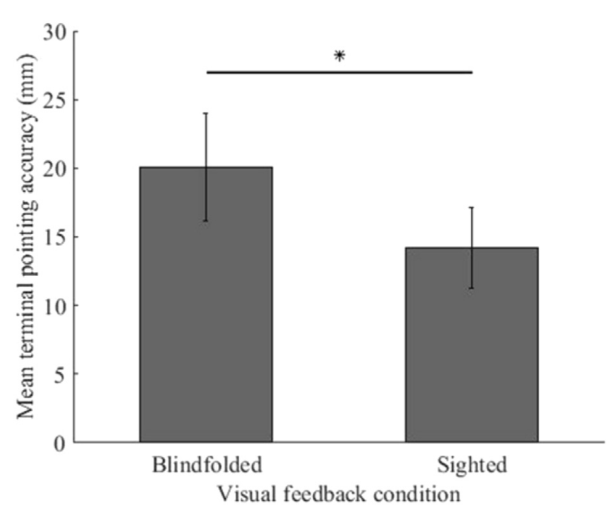

Fig. 4 – The effect of visual feedback on TPA. The figure depicts the mean TPA in millimeters as a function of visual feedback condition. The asterisk indicates a significant difference between blindfolded and sighted conditions. Error bars represent the standard error of the mean (SEM).

3.6. *Frequency of movements terminated at the left and the right targets under internal guidance*

The GEE Poisson regression model revealed that the interaction involving stimulation condition and visual feedback significantly predicted the frequency of movements terminated at the left (generalized score test $\chi^2 = 10.49$, $p = .015$) and the right (generalized score test $\chi^2 = 10.04$, $p = .018$) targets under internal guidance (Fig. 5). This effect was defined by a significant reduction of leftward internally guided movements completed without visual feedback under rMFG stimulation (Risk ratio 1.36, 95% confidence interval 1.12–1.64, $p = .002$). Pairwise comparisons corrected with Bonferroni indicated that, when stimulating the rMFG, the frequency of pointing leftward was significantly reduced under blindfolded conditions ($M = 4.43$, $SD = 1.09$) in comparison to sighted ones ($M = 7.07$, $SD = 1.21$), t (13) = −7.10, $p = .001$. Furthermore, the frequency of pointing leftward under blindfolded conditions proved to be significantly reduced during rMFG stimulation ($M = 4.43$, $SD = 1.09$) as compared to sham [($M = 5.75$, $SD = .75$), t (13) = −3.36, $p = .005$], control [($M = 5.79$, $SD = 1.05$), t (13) = −5.47, $p = .001$], and parietal stimulation conditions [($M = 5.64$, $SD = 1.28$), t (13) = −4.32, $p = .001$]. Additionally, during rMFG stimulation applied under blindfolded conditions, the number of movements terminated at the left target ($M = 4.43$, $SD = 1.09$) was significantly smaller than that of movements terminated at the right target [($M = 7.57$, $SD = 1.09$), t (13) = −5.39, $p = .001$].

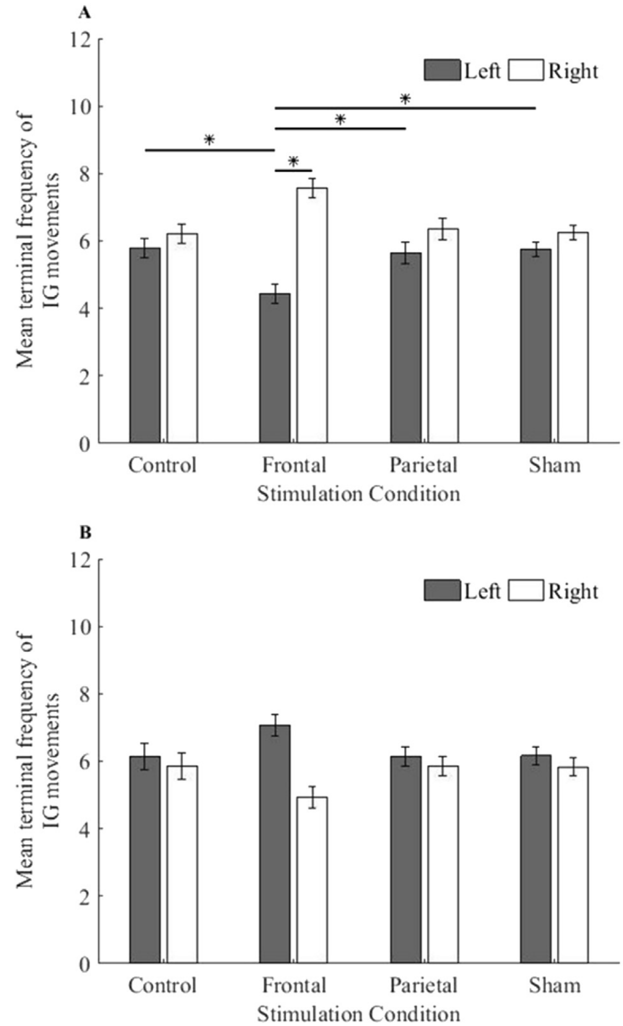

Fig. 5 – The effect of stimulation condition on the frequency of IG movements terminated at the left or the right target under (A) blindfolded and (B) sighted conditions. The figure depicts the mean number of movements as a function of stimulation condition and movement direction. Asterisks indicate significant differences between conditions. Error bars represent the SEM.

3.6.1. *Number of left- and rightward IG movements with corrected initial direction*

The fact that the frequency of leftward and rightward IG movements executed without visual feedback differed at the terminal but not at the initial phase provided an indication that the initial movement direction was corrected during the course of the movement. Consequently, the increased number of rightward IG movements apparently resulted from the redirection of left-intended movements toward the right upon visual feedback removal. In order to confirm this assumption the number of movements whose final direction differed from the initial one was first counted per condition, and a GEE procedure with negative binomial regression was then used to model the number of blindfolded left- and rightward IG movements with corrected initial direction, as a function of stimulation condition. This particular regression model was employed in order to account for the high number of zeros contained in the dependent variable (Allison, 2012; Xie, Tao, McHugo, & Drake, 2013).

The negative binomial regression indicated that the main effect of stimulation significantly predicted the number of movements with corrected initial direction which terminated at the right target (generalized score test $\chi^2 = 11.81$, $p = .008$) under blindfolded conditions. This effect was defined by a significant increase in the number of corrections for blindfolded movements terminated at the right under rMFG stimulation (Risk ratio 14.93, 95% confidence interval 2.43–91.73, $p = .004$) (Fig. 6). In other words, a significant number of IG movements performed during rMFG stimulation were initially intended to the left target but changed their trajectory following the removal of visual feedback (Fig. 7). Bonferroni corrected pairwise comparisons revealed that the number of blindfolded movements with corrected initial direction was significantly higher under rMFG stimulation ($M = 1.36$, $SD = .95$), as compared to that observed under sham [($M = .09$, $SD = .30$), t (13) = 4.90, $p = .001$], parietal [($M = .08$, $SD = .27$), t (13) = 5.33, $p = .001$], and control [($M = .08$, $SD = .28$), t (13) = 3.77, $p = .003$] conditions. Moreover, the number of blindfolded movements with corrected initial direction was found to be significantly smaller for leftward ($M = .23$, $SD = .44$) than for rightward IG movements [($M = 1.31$, $SD = .95$), t (13) = −3.74, $p = .012$], under conditions of rMFG stimulation.

These findings can also be illustrated by the fact that MTs in rightward IG movements conducted during rMFG stimulation showed a trend to be longer than those observed in the other stimulation conditions (Fig. 8A). It is relevant to note

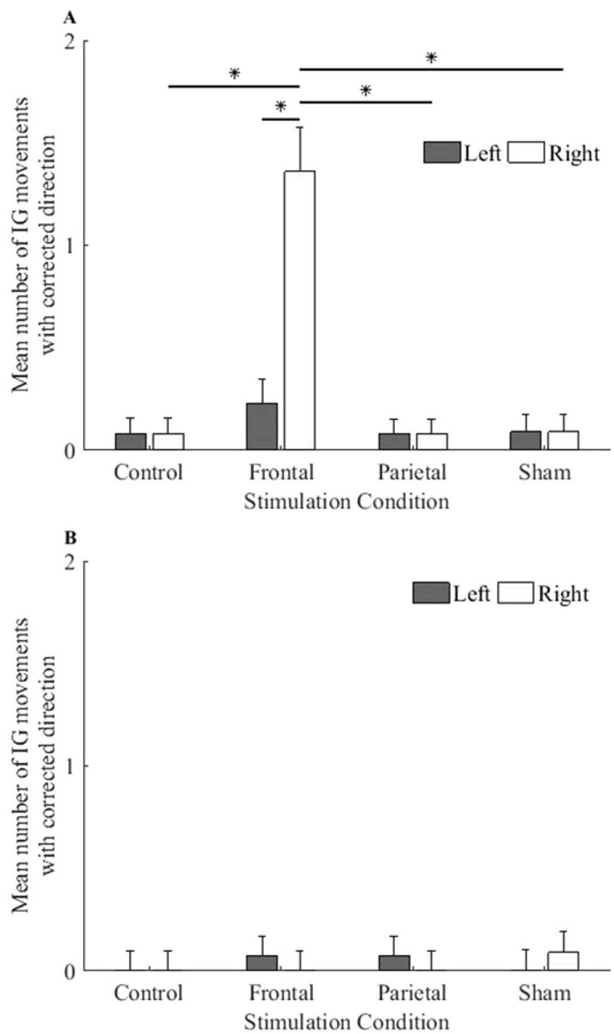

Fig. 6 – The effect of stimulation condition on the number of (A) blindfolded and (B) sighted IG movements with corrected initial direction. The figure depicts the mean number of movements as a function of stimulation condition and movement direction. Asterisks indicate significant differences between stimulation conditions. Error bars represent the SEM.

that although this difference did not reach statistical significance, the interaction among visual feedback, movement direction, and stimulation condition showed a moderate effect size ($\eta_p^2 = .18$) for IG movements.

4. Discussion

Although several neurophysiological and patient studies have acknowledged that DMD might affect the planning and execution of movements to the contralateral space, no clear consensus has been reached regarding their neuroanatomical substrates. To follow up on this line of research, the present study used a TMS virtual lesion approach to examine the involvement of rMFG and rAG in the directional aspects of aiming movements.

Whereas applying rTMS to the rAG prolonged the RTs of contralateral movements under IG conditions, rTMS applied over the rMFG reduced the likelihood of completing IG movements directed toward the left target in conditions where visual feedback was removed at movement onset. The analysis of MTs, TPA and IDEs did not reveal any significant effect from stimulation.

4.1. *Role of rAG in the selection of contralateral movements*

Interestingly, rTMS targeting the rAG prolonged RT exclusively in the IG and not in the EG conditions. This result suggests that, instead of interfering with contralateral movement planning, rTMS applied to the rAG affected the voluntary selection of contralateral movements. Moreover, the absence of rAG stimulation effects on TPA and IDEs provides further evidence that movement planning was not affected.

These findings are in agreement with a recent functional MRI study by Ariani, Wurm, and Lingnau (2015), in which the right intraparietal sulcus (rIPS) was associated with internally driven but not externally driven movement plans. This led the authors to suggest that rIPS is preferentially involved in the selection (i.e., deciding which movement to perform) rather than in the planning of the movement. Considering that during the parietal stimulation condition of our study the coil was positioned over the posterior part of the rAG, adjacent to the rIPS, it is likely that the stimulated area overlapped with that found by Ariani et al. (2015), thus also interfering with action selection processes.

Regarding the contralateral nature of these RTs effects, there is evidence that the representation of the action space in the inferior parietal lobule is highly skewed toward the contralateral workspace (Battaglia-Mayer et al., 2005). Similarly, recent TMS studies using single pulse (Davare, Zénon, Pourtois, Desmurget, & Olivier, 2012; Davare et al., 2015) and paired pulse (Koch et al., 2008) protocols have indicated that areas within the left or right inferior parietal lobule (i.e., AG or intraparietal sulcus) encode preparatory signals for movements directed toward targets located in the contralateral space. Most importantly, such preparatory activity was only observed at specific time points following the presentation of the imperative signal to start the movement. Considering that our stimulation protocol lacked such temporal specificity, there is a possibility that, because we presented the first TMS pulse simultaneously with the imperative auditory cue, the interference effects occurred at an earlier stage of the movement, namely when selecting movement direction. In line with this interpretation, it might be speculated that the preference of right inferior parietal areas for contralateral movements might involve not only movement planning but might also affect decision making, a function that works together with action selection. Such an idea would be supported by the indication that decision making and sensorimotor control systems are highly integrated in the brain (Lepora & Pezzulo, 2015; Wolpert & Landy, 2012). It should be noted that we are not aware of any previous TMS study exploring DMD in the context of internally guided movements.

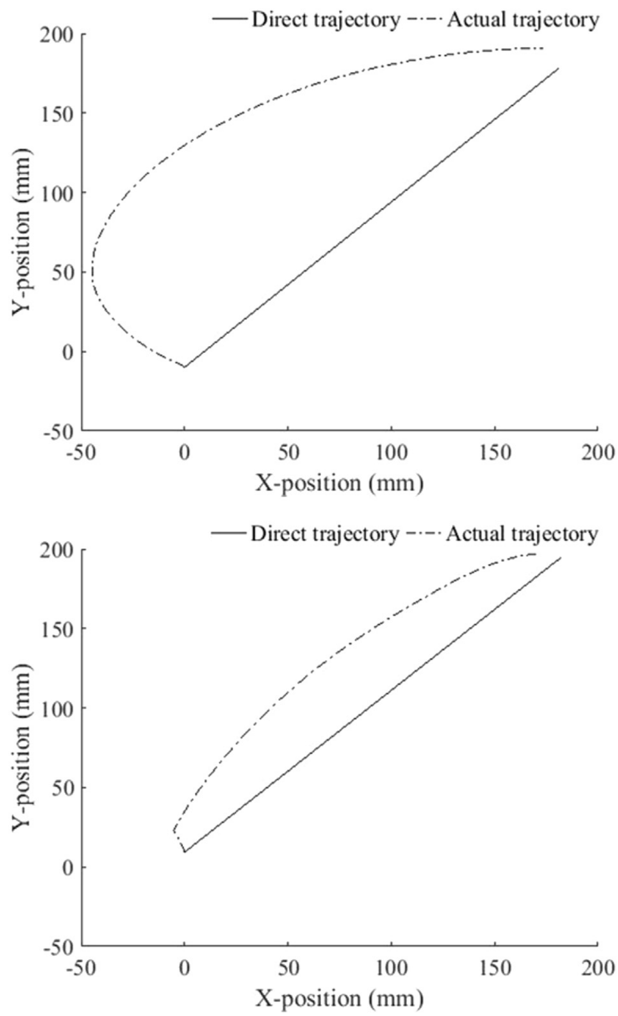

Fig. 7 – Hand trajectories during two exemplar trials of rightward IG-blindfolded movements that were initially directed to the left.

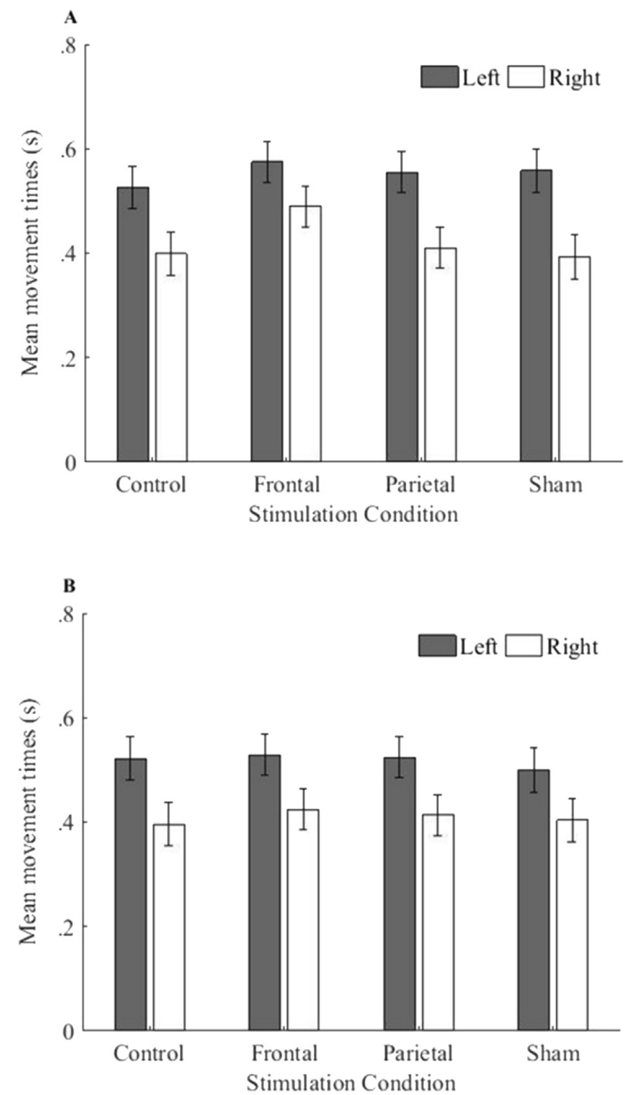

Fig. 8 – The effects of stimulation condition on movement times for IG movements conducted under (A) blindfolded and (B) sighted conditions. The figure illustrates the mean movement times in seconds as a function of stimulation condition and movement direction. Error bars represent the SEM.

4.2. *Role of the rMFG in completing contralateral movements*

As expected, rMFG stimulation reduced the frequency of leftward IG movements. More specifically, rMFG stimulation reduced the likelihood of completing movements directed toward the left target in conditions where visual feedback was removed at movement onset. This behavior is comparable to the symptoms of reduced spatial exploration or directional impersistence described in the context of neglect (Heilman, 2004). Some studies have suggested that rightward biases attributed to intentional motor deficits may become particularly evident when the targets are not visible (Fink & Marshall, 2005; Harvey, 2004; Làdavas, Umiltà, Ziani, Brogi, & Minarini, 1993). Likewise, patients performing cancellation tasks without visual feedback increasingly omitted left targets and repeatedly canceled stimuli toward the ipsilesional side (Làdavas et al., 1993; Parton et al., 2006; Wansard et al., 2014).

The effect of rMFG stimulation on leftward pointing frequency under internal guidance might be explained by a decline in the level of commitment to the initial decision to move toward the left (Cisek & Pastor-Bernier, 2014; Lepora & Pezzulo, 2015). The stimulation might have weakened the value of the contralateral action, making it difficult to persist in completing leftward movements in conditions where visual feedback was not provided during movement execution. Thus, although participants were able to make the initial decision to move toward the left, such a decision was not strong enough to resist the high level of sensory uncertainty, prompting a change of mind halfway through the movement (Resulaj, Kiani, Wolpert, & Shadlen, 2009). Moreover, the higher biomechanical costs of leftward movements as opposed to rightward ones (Flanagan & Lolley, 2001; Personnier, Paizis, Ballay, & Papaxanthis, 2008) might have been instrumental in causing blindfolded leftward movements to require higher executive control. These interpretations are in line with an embodied choice model of decision making, in which action and its dynamics are considered an integral part of the decision making process (Lepora & Pezzulo, 2015).

Another possible interpretation of the effect of rMFG stimulation has to do with the working memory load, which might have differed between blindfolded and sighted conditions. Assuming that the condition without visual feedback required more spatial working memory resources than the condition with visual feedback, it is likely that the interference in rMFG affected the short-term memory representation of the contralateral target. This idea is consistent with evidence showing that neglect patients exhibit short-term memory deficits, which tend to be worse in the contralesional field (Corbetta & Shulman, 2011; Kristjánsson & Vuilleumier, 2010). Furthermore, it would be in agreement with a recent fMRI study suggesting that the rMFG is involved in the interaction between ventral and dorsal attention systems (Corbetta, Patel, & Shulman, 2008; Vossel, Geng, & Fink, 2013), therefore playing a crucial role in engaging top-down control (Japee, Holiday, Satyshur, Mukai, & Ungerleider, 2015). Such a role certainly becomes more relevant when a biomechanically complex movement is performed in the absence of visual feedback.

To conclude, several factors would explain the weakened decision to perform leftward movements under rMFG stimulation, increasing the likelihood of changes of mind upon visual feedback removal. This explains that the frequency of leftward IG movements was reduced in the final phase of the movement but not at its onset when visual feedback was always available. A question for further research is whether the initial decision could be affected when visual feedback is removed shortly before the presentation of the imperative cue. This could result in a reduced frequency of IG movements already at movement onset.

4.3. *Concluding remarks*

The stimulation of rAG and rMFG did not seem to directly affect movement planning or execution processes during directional aiming movements. It rather appeared to interfere with decision making processes. As for the occurrence of direction specific deficits, the disruption of both areas seemed to influence contralateral IG movements. Such directional specificity was, however, more explicit during the parietal stimulation condition, in which the stimulation interfered with the decision to move toward the left target, causing longer RTs. Conversely, frontal stimulation effectively reduced the likelihood to complete leftward IG movements only upon visual feedback removal. This suggested a change in decision, indicated by the observed redirection of movements. Taken together, these results might suggest that rAG stimulation affected the initial selection of leftward movements, whereas rMFG stimulation interfered with control processes required to maintain the goal and commit to the decision to move toward the left under conditions of high sensory uncertainty.

The character of the induced effects might be attributed to our stimulation protocol. Considering that the timing of the first pulse was not varied but always occurred in parallel with the imperative cue, it is likely that the selection of the movement rather than its planning or execution was predominantly affected. This would explain that only internally guided movements were disrupted under both stimulation conditions. In any case, this experiment led us to observe that contralateral deficits resulting from rAG and rMFG disruption might potentially affect the selection, value and/or short-term memory representation of leftward movements. Future TMS studies should aim at determining the functional relations of MFG and AG to sensorimotor and cognitive processes during different stages of motor control.

Conflict of interest

The authors declare no conflict of interest.

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4 Neuroanatomical and behavioral factors associated with the effectiveness of two weekly sessions of prism adaptation in the treatment of unilateral neglect

This chapter includes a research article entitled "Neuroanatomical and behavioral factors associated with the effectiveness of two weekly sessions of prism adaptation in the treatment of unilateral neglect". This article suggests that the capacity to adapt proprioceptively strongly to rightward deviating prisms might be effective in correcting the biased performance in neuropsychological tasks with a high motor involvement. It also shows that the integrity of temporo-parietal areas together with the damage of frontal and subcortical areas might support the effectiveness of prism adaptation. The manuscript was accepted for publication in Neuropsychological Rehabilitation in March 2018 and recently entered the production phase.

Contributions:

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The author of this thesis is the first author of the manuscript; S.S. conceived, designed, and supervised the study; S.S, M.G.-H., and S.E. recruited patients and conducted the study protocol; M.G.-H. and S.S contributed equally to data' analysis, results' interpretation, and manuscript's writing; J.H. provided critical feedback on the manuscript, which was further commented by I.K. and S.E.

Neuroanatomical and behavioral factors associated with the effectiveness of two weekly sessions of prism adaptation in the treatment of unilateral neglect

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Abstract

Among the different interventions to alleviate the symptoms of unilateral neglect, prism adaptation (PA) appears especially promising. To elucidate the contribution of some neuroanatomical and behavioral factors to PA's effectiveness, we conducted a study combining neuropsychological and lesion mapping methods on a group of 19 neglect patients who underwent two sessions of PA during one week and assessed their improvement relative to the baseline until the following week (7 to 8 days later). Correlation analyses revealed a significant positive relationship between the magnitude of the proprioceptive after-effect and the improvement at the follow-up session in two perceptual tasks requiring motor responses. Conversely, no correlation was found between the proprioceptive after-effect and the improvement in a perceptual task with no motor involvement. This finding suggests that patients' potential to show a prism-related improvement in motor related tasks might be indicated by the strength of their proprioceptive response (proprioceptive after-effect). As to the neuroanatomical basis of this relationship, subtraction analyses suggested that patients' improvement in perceptual tasks with high motor involvement might be facilitated by the integrity of temporo-parietal areas and the damage of frontal and subcortical areas.

Keywords: Unilateral neglect; prism adaptation; cancellation tasks; landmark task; lesion analysis.

Introduction

Unilateral neglect is a disabling neuropsychological disorder commonly associated with right-brain injury, which is characterized by the inability to detect, respond, or orient toward stimuli located in the contralesional side of space (Heilman, Valenstein, & Watson, 1984). Among other behaviors, patients with unilateral neglect may not be able to react to a person addressing them from their left or may constantly bump into objects located on their left when walking or navigating with the wheelchair. It is estimated that up to 50% of right-hemisphere stroke survivors may exhibit neglect symptoms (Buxbaum et al., 2004), which in approximately 37% of the cases may persist chronically (Farnè et al., 2004). Moreover, the occurrence of this disorder has been associated with poor functional prognosis (Di Monaco et al., 2011; Katz, Hartman-Maeir, Ring, & Soroker, 1999), decreased likelihood of rehabilitation success (Shulman et al., 2015) and longer hospitalization periods (Gillen, Tennen, & McKee, 2005). In an attempt to reduce the disabling effects of neglect, many different rehabilitation approaches have been developed (Luauté, Halligan, Rode, Rossetti, & Boisson, 2006). Among them, the exposure to right-shifting prismatic goggles, known as prism adaptation (PA), has proven especially useful in the treatment of this disorder (Newport & Schenk, 2012; Rode et al., 2015).

Patients undergoing PA wear goggles that displace their visual field to the right by a certain angle (typically 10°) while performing series of aiming movements toward targets located to the left and to the right of the sagittal midline. At first, their movements become inaccurate and targets are missed in the direction of the displacement. However, after a few trials patients learn to counteract the displacement by reaching slightly to the left of the perceived target location. This corrective behavior persists for some time after the goggles have been removed (Farnè, Rossetti, Toniolo, & Ladavas, 2002; Rossetti et al., 1998). The strength of this correction is typically expressed as the after-effect, which can be quantified by means of different parameters, namely, the proprioceptive shift (Jacquin-Courtois et al., 2013), the visual shift, and the total shift (Bultitude et al., 2016; Jacquin-Courtois et al., 2013; Rode et al., 2015). The first two parameters are generally assessed by comparing straight-ahead judgements of patients immediately before and after the adaptation procedure, yet following different procedures. When assessing the proprioceptive shift, patients perform pointing movements in the straight-ahead direction with their index finger either blindfolded or in the darkness. To assess the visual shift, on the other hand, patients are asked to interrupt the movement of a visual target moving laterally as soon as they judge that the target has reached a straight-ahead position. As for the assessment of the total shift, patients carry out a sequence of pointing movements in the direction of a visual target without seeing their hand (Rode et al., 2015).

The evidence that PA might be one of the most promising methods in the rehabilitation of unilateral neglect has motivated a number of studies to explore potential neuroanatomical and behavioral aspects associated with a higher chance of intervention's success (Chen, Goedert, Shah, Foundas, & Barrett, 2014; Luauté et al., 2006; Rode et al., 2015; Sarri et al., 2008; Serino, Angeli, Frassinetti, & Ladavas, 2006; Striemer & Danckert, 2010). This aim has been further encouraged by indications of reduced or even lacking responses to PA in some patients (Mizuno et al., 2011; Serino, Barbiani, Rinaldesi, & Ladavas, 2009).

As to the neuroanatomical aspects related to PA's success, studies have reported diverse findings. For instance, the integrity of a wide number of regions including cerebellar (Luauté et al., 2006; Panico, Sagliano, Grossi, & Trojano, 2016), parietal (Luauté et al., 2006; Sarri et al., 2008; Striemer & Danckert, 2010), temporal (Chen et al., 2014), occipital (Serino et al., 2006) and frontal cortices (Sarri et al., 2008) has been considered important. Interestingly, recent evidence has pointed to the presence of frontal lesions as a potential predictor of functional improvement after PA (Chen et al., 2014; Gossmann, Kastrup, Kerkhoff, López-Herrero, & Hildebrandt, 2013).

Similarly, research on the behavioral aspects associated with PA's success has provided varied findings. One aspect, which has been particularly debated, refers to the predominant influence of PA on motor-intentional or directional motor deficits. Several studies have indicated that the counteracting effect of PA on the performance biases exhibited by patients with neglect (Fortis, Chen, Goedert, & Barrett, 2011; Goedert, Chen, Boston, Foundas, & Barrett, 2013; Striemer & Danckert, 2010) and healthy participants (Fortis, Goedert, & Barrett, 2011; Striemer, Russell, & Nath, 2016) might be particularly evident in tasks aimed to assess directional motor deficits (e.g. line bisection, motor versions of the landmark task; Saevarsson, 2013) as compared to those mainly assessing perceptual ones (e.g. perceptual version of the landmark task). Consequently, it has been suggested that PA primarily affects the directional motor component of neglect. Nevertheless, this idea has been challenged by studies reporting that PA might not only improve performance in motor related tasks but also in those requiring mental imagery and visual search (Rode, Rossetti, Li, & Boisson, 1998; Saevarsson, Kristjánsson, Hildebrandt, & Halsband, 2009; Vangkilde & Habekost, 2010). To make things even more complicated, there have been a few studies, which regardless of the differentiation between motor and visual or perceptual deficits have found no evidence of positive therapeutic effects of PA on patients' performance in functional and paper-and-pencil tests. Accordingly, these studies have suggested that learning and attentional factors attributed to the repetition of tests might account for the favorable outcomes described by previous studies (Nys, de Haan, Kunneman, de Kort, & Dijkerman, 2008; Rousseaux, Bernati, Saj, & Kozlowski, 2006; Turton, O'Leary, Gabb, Woodward, & Gilchrist, 2010). However, it is important to note that the null results reported by these studies might have resulted from methodological differences including among others, the probable insufficient magnitude of the prism's deviation (Turton et al., 2010), and the enrollment of patients with acute neglect symptoms (Nys et al., 2008).

An additional behavioral aspect, which has been subject of controversy, pertains to whether the magnitude of the after-effect might relate to and possibly predict the extent of improvement in neglect symptoms following PA. Some studies have indeed indicated a positive relation between them (Farnè, Rossetti, Toniolo, & Ladavas, 2002; Sarri et al., 2008; Striemer et al., 2016). However, other studies have described cases of patients showing improvements despite not having experienced any after-effect and vice versa (Frassinetti, Angeli, Meneghello, Avanzi, & Ladavas, 2002; Pisella, Rode, Farnè, Boisson, & Rossetti, 2002). It should be underlined that the general term after-effect has sometimes been indifferently used to refer to the total or the proprioceptive after-effect. This misuse has led to the misconception that the after-effect is essentially associated with the improvement in neglect symptoms.

The present study aimed to shed light on some of the controversies surrounding the neuroanatomical and behavioral aspects related to PA's effectiveness. To this aim, we conducted a study combining neuropsychological and lesion mapping methods on a group of 19 neglect patients who underwent a two-week PA protocol consisting of two sessions of intervention and one session of follow-up assessment. Two separate sessions of intervention per week have been suggested by previous studies as being the minimal number required to obtain long-lasting therapeutic effects (Jacquin-Courtois et al., 2013; Rode et al., 2015). Three main research objectives were addressed. First, we examined whether the magnitude of the proprioceptive shift exhibited in the first session might relate to any potential improvement in neuropsychological performance across sessions. The reason why we used this parameter to quantify the after-effect is that it is known to provide a more robust and reliable measure closely related to the pathological rightward biases in the subjective straight-ahead, frequently exhibited by neglect patients (Rode et al., 2015; Weiner, Hallett, & Funkenstein, 1983). Provided that there was an indication of neuropsychological improvement, we examined whether it might be predominantly observed in tasks requiring a motor response. The protocol for neuropsychological assessment included tasks with varying degrees of motor involvement. In order from the highest to the lowest motor involvement, we employed a manual (motor) version of the landmark task, four cancellation tasks taken from the Behavioral Inattention Test (BIT), and a verbal version of the landmark task. Furthermore, we explored whether certain lesion patterns might be identified in patients showing a higher improvement in neuropsychological performance and in those showing a lower one.

Methods

Participants

Twenty-four patients diagnosed with left unilateral neglect secondary to right hemispheric stroke gave written informed consent to take part in the present study. All patients were right-handed and had normal or corrected-to-normal vision. A neuropsychological assessment including four cancellation tasks and two adapted versions of the landmark task (manual and verbal; Capitani, Neppi-Mòdona, & Bisiach, 2000) was performed in the first session to confirm the diagnosis of neglect and get an impression of the severity of impairment at baseline. Additionally, a short clinical examination was conducted to test for motor and visual field deficits. Ten patients presented with complete left homonymous hemianopia on confrontation. Furthermore, all except two patients exhibited some degree of hemiplegia or hemiparesis of the left side. Only patients with lesions limited to the right hemisphere, who exhibited a high number of omissions of left-sided stimuli on the cancellation tasks and who had no history of previous strokes, were included in the study. Otherwise, patients showing ceiling performances in most of the tasks or suffering from any other neurological condition were excluded from it. Consequently, the sample comprised a total of 19 patients (mean age 65.6 S.D. = 9.4, eight females and eleven males). Of these patients, thirteen were in the chronic stage (at least 12 weeks post-stroke, mean number of weeks 19) and six in the post-acute stage (at least 8 weeks post-stroke, mean number of weeks 9). Details of age, time post-stroke, lesion site and etiology are given in Table 1. This study was conducted in accordance with the declaration of Helsinki and the experimental protocol was approved by the Ethics Committee of the Medical Faculty of the Technical University of Munich (registration number: 5838/13).

Table 1. Summary of patients' clinical and demographic data

Patient	Gender	Age	Time between stroke and study (weeks)	Etiology	Lesion size (cc)	Lesion site
1	F	74	22	Hemorrhagic stroke	226.14	Occipital, temporal, insula, parietal, basal ganglia, cerebellum
2	M	55	10	Ischemic stroke	98.94	Parietal, occipital, cerebellum
3	F	63	18	Hemorrhagic stroke	136.91	Parietal, occipital, temporal, cerebellum
4	M	64	17	Hemorrhagic stroke	94.13	Frontal, temporal, insula, basal ganglia
5	F	43	20	Ischemic stroke	87.34	Frontal, occipital, parietal
6	F	69	31	Hemorrhagic stroke	145.60	Frontal, parietal, temporal, insula, basal ganglia
7	F	70	13	Ischemic stroke	159.54	Frontal, parietal, temporal, insula, basal ganglia
8	F	58	29	Hemorrhagic stroke	105.22	Frontal, temporal, occipital, insula, basal ganglia

9	M	59	26	Hemorrhagic stroke	148.74	Frontal, temporal, occipital, parietal, insula
10	M	68	16	Ischemic stroke	105.53	Parietal, occipital, temporal, insula
11	M	53	9	Ischemic stroke	233.87	Frontal, parietal, occipital, temporal, basal ganglia
12	M	72	8	Ischemic stroke	105.78	Frontal, parietal, temporal, insula, basal ganglia
13	F	73	8	Hemorrhagic stroke	229.24	Frontal, parietal, temporal, basal ganglia
14	M	74	12	Ischemic stroke	42.57	Temporal, occipital
15	M	74	11	Ischemic stroke	104.83	Frontal, parietal, temporal, basal ganglia
16	M	70	15	Ischemic stroke	37.79	Occipital, temporal
17	M	73	17	Hemorrhagic stroke	34.10	Occipital
18	M	56	12	Hemorrhagic stroke	156.24	Frontal, occipital, parietal, temporal, insula
19	F	79	8	Ischemic stroke	197.53	Frontal, parietal, temporal, insula, basal ganglia

Procedure

Patients underwent a three session protocol over a period of eight to nine days, including two sessions of neuropsychological assessment combined with PA (first and fourth day), and one follow-up session consisting of assessment only (eighth or ninth day). To control for any order effects, the order of the assessment and the intervention was alternated across sessions, with the former preceding the latter in the first session, and the other way around in the second session.

Neuropsychological assessment

The assessment protocol included four cancellation tasks (line, star, letter, and number cancellation), and two versions of the landmark task (manual and verbal) adapted from the protocol employed by Vossel, Eschenbeck, Weiss, & Fink, (2010) and Bisiach, Ricci, Lualdi, & Colombo, (1998). The order of tasks was counterbalanced across sessions. The Landmark task consisted of 9 trials in which a pre-bisected horizontal line (180 mm long and 1 mm thick) was presented on a sheet of A4 paper aligned to the patients' sagittal midline. The bisection mark was located either at the center of the line (line E in Figure 1) or 5, 15, 30 or 60 mm to the left or to the right from it (Figure 1). In the verbal version of the task (LM-V) patients were instructed to judge verbally whether or not the bisection mark was located centrally. Conversely, in the manual version of the task (LM-M) patients used a pen to mark the line at the point where they considered the true center was. It should be noted that this manual version resembles a line bisection task, with the only difference being that the lines were pre-bisected. By doing so we aimed to make the verbal and the manual versions as perceptually comparable as possible (Saevarsson & Kristjánsson, 2013).

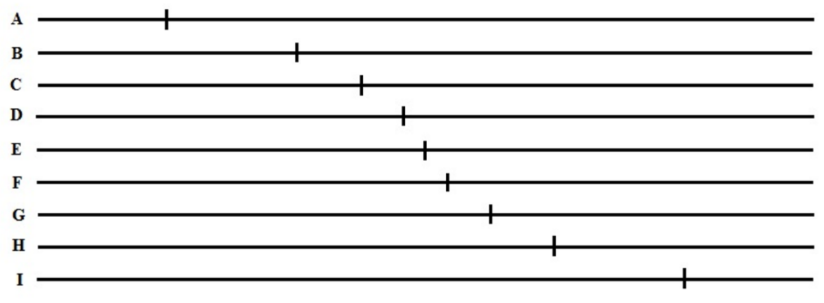

Figure 1. Schematic illustration of the nine pre-bisected lines presented in both versions of the landmark task.

Prism adaptation intervention and assessment of the proprioceptive after-effect

For the PA procedure we used a wooden frame (height 41 cm, depth 30 cm, width 80 cm) with a height-adjustable top board serving as chin rest (cf. Rode et al., 2015; Rossetti et al., 1998). While wearing prism glasses that displaced their visual field rightward by 10 degrees, patients performed a series of 60 pointing movements with the right hand toward two targets located laterally to their body midline (i.e. 21° to the right and to the left and 50 cm away). Movements were initiated upon verbal command of the experimenter and alternated pseudo-randomly between both targets. During prism exposure, the top board prevented patients from seeing the first 30 to 50% of the pointing movement. By occluding the first half of the hand's trajectory a proprioceptive-visual coding of the movement was facilitated (Rode et al., 2015; Rossetti, Desmurget, & Prablanc, 1995). Patients were asked to keep their right hand on a circular protruding button aligned with their sagittal midline (hand starting position) in between trials. In order to measure the adaptation after-effect during the two sessions of intervention, patients completed 10 straight-ahead judgements while blindfolded immediately before (pre-adaptation) and after the adaptation trials (post-adaptation). Patients' performance was videotaped and subsequently assessed by the experimenter, who registered the pointing deviation with respect to the sagittal axis. To this end a grid pattern (8 x 16, 5 cm squares) traced on a plastic sheet attached to the external edge of the lower board and extended across the table was used as reference. A measurement scale (range from -40 to 40 cm) extending from the most distant side of the grid and with the zero point aligned with the patient's mid-sagittal axis was used to calculate the lateral deviation of the straight-ahead judgements. To assure the accuracy of the assessment, while videotaping patients' performance the experimenter employed a ruler to project the end-point position of the finger onto the corresponding point in the measurement scale. Rightward deviation was coded with positive values and leftward deviation was coded with negative ones. These values were converted into angular degrees from the sagittal axis and the after-effect was then indicated by the difference between the pre- and the post-adaptation deviation's degrees.

Data analysis

Patients' performance on each of the cancellation tasks was quantified by means of the laterality score computed following the procedure described by Bartolomeo & Chokron, (1999). As to the two versions of the landmark task, patients' performance was measured in terms of the mean percentage deviation from the real center of the line. For the verbal version, the subjective center was determined by averaging the percentage deviation of those trials in which patients judged the bisection mark to be centrally located.

To confirm the presence of a proprioceptive after-effect in the first intervention session, a paired sample *t*-test comparing the mean pointing deviation during the pre- and the post-adaptation phases was conducted for the whole group of patients. Since four patients dropped out after the first session due to tiredness, unwillingness to continue or a decline in their health status, fifteen patients with complete data were included in the following analyses. The presence of an after-effect was also examined in the second intervention session by means of a paired-sample *t*-test. Additionally, to examine the temporal evolution of the subjective straight-ahead across sessions a repeated-measures analysis of variance (ANOVA) was performed on the straight-ahead judgement, with session (three levels: baseline, second post-adaptation and follow-up) as within-subject factor.

Additionally, in order to assess whether the magnitude of the initial proprioceptive after-effect could relate to any amelioration of neglect symptoms, correlation analyses were conducted to explore the relationship between the after-effect and the changes in performance on the cancellation and the landmark tasks. To this purpose, we estimated two indexes of improvement for each task by subtracting the scores in the second and follow-up sessions from the baseline and correlated them with the proprioceptive after-effect displayed in the first session. A positive index score indicated an improvement in performance. Considering that the data of one patient was detected as a significant outlier in the after-effect of the first and the second sessions, fourteen patients were included in these analyses. Values greater than 1.5 times the interquartile range were regarded as outliers (fist session: 19.1; second session: 27).

Lesion mapping and analysis

Brain lesions were confirmed in all 19 patients by means of MRI (magnetic resonance imaging) and structural CT (computed tomography) scans. MRI scans were available for nine patients and CT scans for 10. Using the MRIcron software (Rorden, Karnath, & Bonilha, 2007), a trained researcher blinded to patients' neuropsychological performance delineated the lesion borders on a slice-by-slice basis, either directly onto the *T2*-weighted fluid-attenuated inversion recovery image (FLAIR; 5-mm slice thickness) or onto the CT scan (2.5-mm slice thickness). In order to examine a three-dimensional lesion, the resulting two-dimensional map was then converted into a volume of interest (VOI). Subsequently, both the anatomical scan together with the lesion volume were normalized to a standard brain template created from older adults using the Clinical Toolbox (Rorden et al, 2012) running under SPM8 (Statistical Parametric Mapping Software package; http://www.fil.ion.ucl.ac.uk/spm). This toolbox provides age-specific templates oriented in MNI space for both CT and MRI scans (Rorden, Bonilha, Fridriksson, Bender, & Karnath, 2012). If available, high-resolution *T1*-weighted anatomical scans were co-registered with the MRI scans during the normalization process. The amount of lesion overlap among all patients is shown in Figure 2.

Afterwards, patients were divided into two groups based on whether they showed a high or a low improvement in the neuropsychological tasks until the follow-up session. To this aim, median splits were calculated on the indexes of neuropsychological improvement previously described (LM-M: Mdn 3.65; LM-V: Mdn 1.17; cancellation tasks: Mdn 0.13), and two groups were defined for each of the tasks. Then, it was evaluated if the group assignment coincided among two or three tasks. Since this was the case for the classification of the LM-M task and the composite score of the cancellation tasks, their corresponding group assignment was used for the following analyses. Overlap images of the lesion maps were first created separately for the two groups of patients and then subtracted from each other in order to identify regions that were predominantly damaged in patients showing a high improvement but mostly spared in those showing a low improvement, and the other way around (Gossmann et al., 2013).

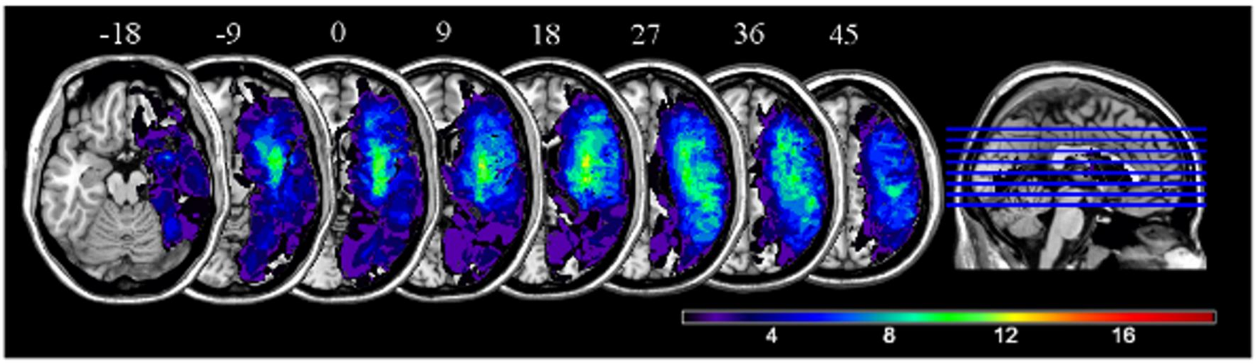

Figure 2. Overlay lesion plot of all neglect patients (*n* = 19). The number of overlapping lesions is illustrated by colors coding increasing frequencies from violet (*n* = 1) to red (*n* = 19). The MNI *z*-coordinates of the axial sections are given.

Results

Proprioceptive after-effect

Bonferroni-corrected paired-sample *t*-tests comparing the subjective straight-ahead judgement immediately before and after the adaptation trials indicated that the mean pointing deviation shifted significantly toward the left following the first (t (18) = 3.68, p = .004, d = .84, 95% CI [2.09, 7.67]; see Figure 3) and the second interventions (t (14) = 2.75, p = .032, d = .71, 95% CI [1.64, 13.33]; see Figure 3). Therefore, as a group, patients did exhibit a proprioceptive after-effect. However, when looking at the individual magnitudes there were three patients whose performance during both interventions got slightly worse (Figure 4). For instance, in the first session their subjective straight-ahead judgement deviated further to the right after the adaptation trials (pat 1: before: 4.3°, after: 8.5°; pat 2: before: 27.1°, after: 30.4°; pat 3: before: 1°, after: 4°).

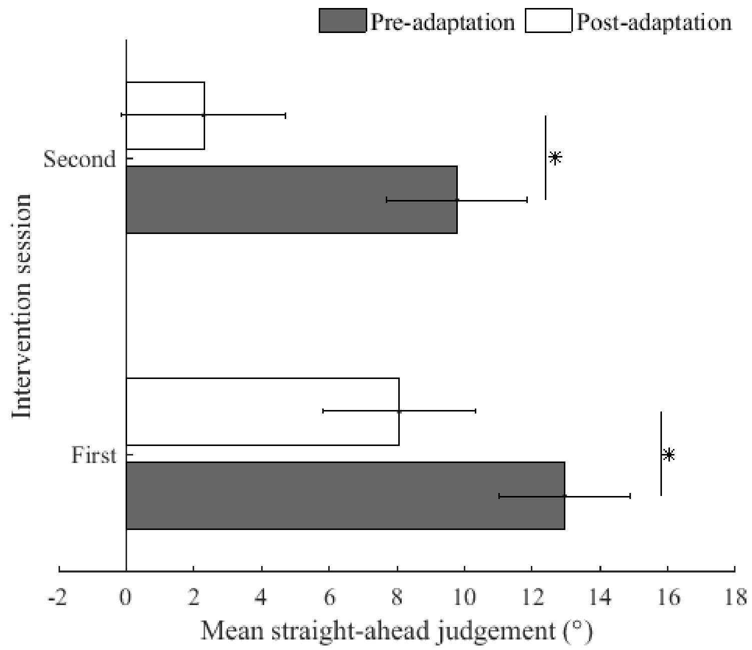

Figure 3. Mean pointing deviation before and after the prism intervention during the first (n =19) and second (n = 15) sessions. The values on the x-axis represent the straight-ahead judgement in angular degrees from the sagittal axis. Error bars represent the standard error of the mean (SEM). The asterisks indicate significant differences between intervention phases.

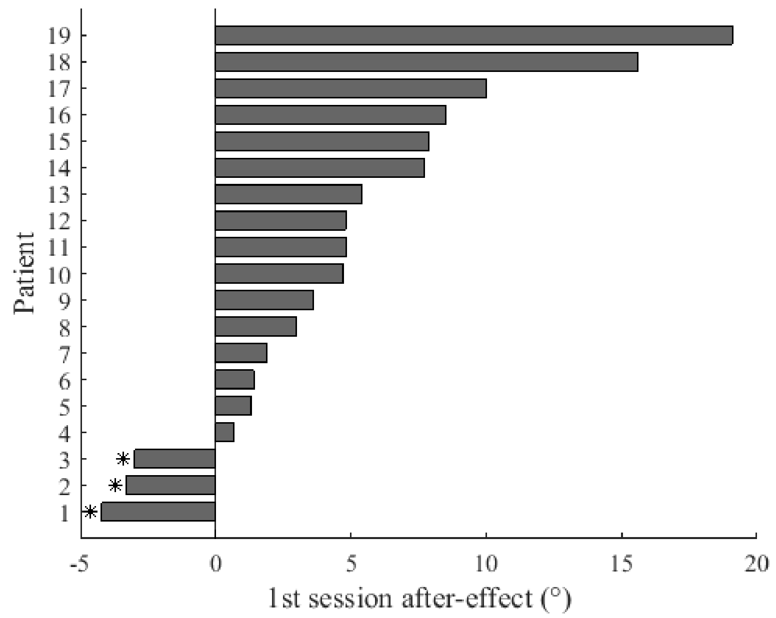

Figure 4. Magnitude of the proprioceptive after-effect for each individual patient. The values on the x-axis represent the difference between the pointing deviation before and after the first prism intervention (pre- minus post-adaptation) in angular degrees from the sagittal axis. Asterisks indicate patients whose straight-ahead judgement in the post-adaptation deviated further to the right.

Evolution of the straight-ahead judgement across sessions

The repeated-measures ANOVA on the straight-ahead judgement revealed a main effect of session (F (2, 28) = 9.39, p = .001, η_p^2 = .40). Pairwise t-tests corrected with Bonferroni indicated that the mean straight-ahead judgement observed in the post-adaption phase of the second session (M: 2.29° SE: 2.43°) was significantly reduced as compared to that observed in the baseline (M: 13.65° SE: 2.35 °; t (14) = 4, p = .002, d = 1.03, 95% CI [5.27, 17.44]) (Figure 5). As for the corrected comparison between the baseline and the follow-up session (M: 8.38° SE: 2.67°), there was a non-significant reduction of the straight-ahead judgement in the latter t (14) = 1.84, p = .16, 95% CI [-0.88, 11.42].

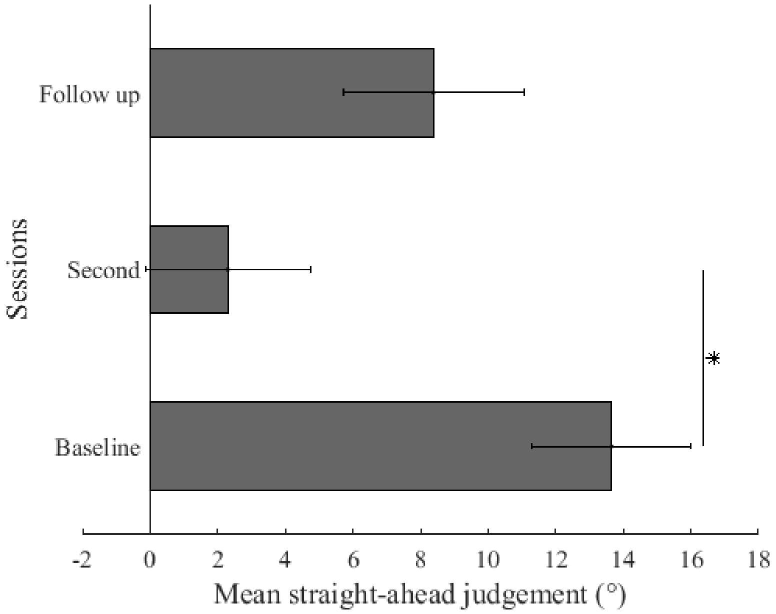

Figure 5. Temporal evolution of the straight-ahead judgement across sessions. The figure depicts the mean straight-ahead judgement in angular degrees from the sagittal axis as a function of sessions. The asterisk indicates a significant difference between sessions. Error bars represent the standard error of the mean (SEM).

Proprioceptive after-effect and its relation to neuropsychological improvement

Since the laterality scores of all four cancellations tasks were highly interrelated (*r* (18) = .70, *p* = .01), a composite score was used for the analyses. Correlation analyses revealed that the magnitude of the proprioceptive after-effect in the first session was significantly associated with an improvement in performance from the baseline up to the follow-up session on the LM-M task (*r* (13) = .77, *p* = .001, 95% CI [.40, .92]); Figure 6.A) and on the cancellation tasks (*r* (13) = .76, *p* = .001, 95% CI [.39, .92]; Figure 6.B). After correcting for multiple comparisons using Holm's adjustment both correlations remained significant (*p* = .03 and *p* = .03 respectively). Similar results were obtained for the correlation (Holm's corrected) between the magnitude of the proprioceptive after-effect in the second session and the improvement in performance at the follow-up session (LM-M task: *r* (13) = .75 *p* = .04, 95% CI [.36, .92]; Cancellation tasks: *r* (13) = .80 *p* = .01, 95% CI [.46, .93]). As to the LM-V task, no significant correlation was observed between its improvement at follow-up and the magnitude of the proprioceptive after-effect at the first (LM-V task: *r* (13) = -.33 *p* = .25, 95% CI [-.73, .24]) or the second session (LM-V task: *r* (13) = -.24 *p* = .40, 95% CI [-.69, .33]). Furthermore, no significant correlation was found between the improvement in performance at the second session and the after-effect at the first (LM-M task: *r* (13) = .37 *p* = .56 , 95% CI [-.19, .76]; LM-V task: *r* (13) = -.48 *p* = .42 , 95% CI [.80, .07]; Cancellation tasks: *r* (13) = .58 *p* = .18 , 95% CI [.07, .85]) or the second session (LM-M task: *r* (13) = .32 *p* = 1 , 95% CI [-.25, .73]; LM-V task: *r* (13) = -.42 *p* = 1 , 95% CI [-.78, .14]; Cancellation tasks: *r* (13) = .44 *p* = 1 , 95% CI [-.12, .78]). On the other hand, there was a significant correlation between the improvement in the LM-M and the cancellation tasks at the follow-up session, *r* (13) = .85 *p* = .001, 95% CI [.59, .95], Figure 7.

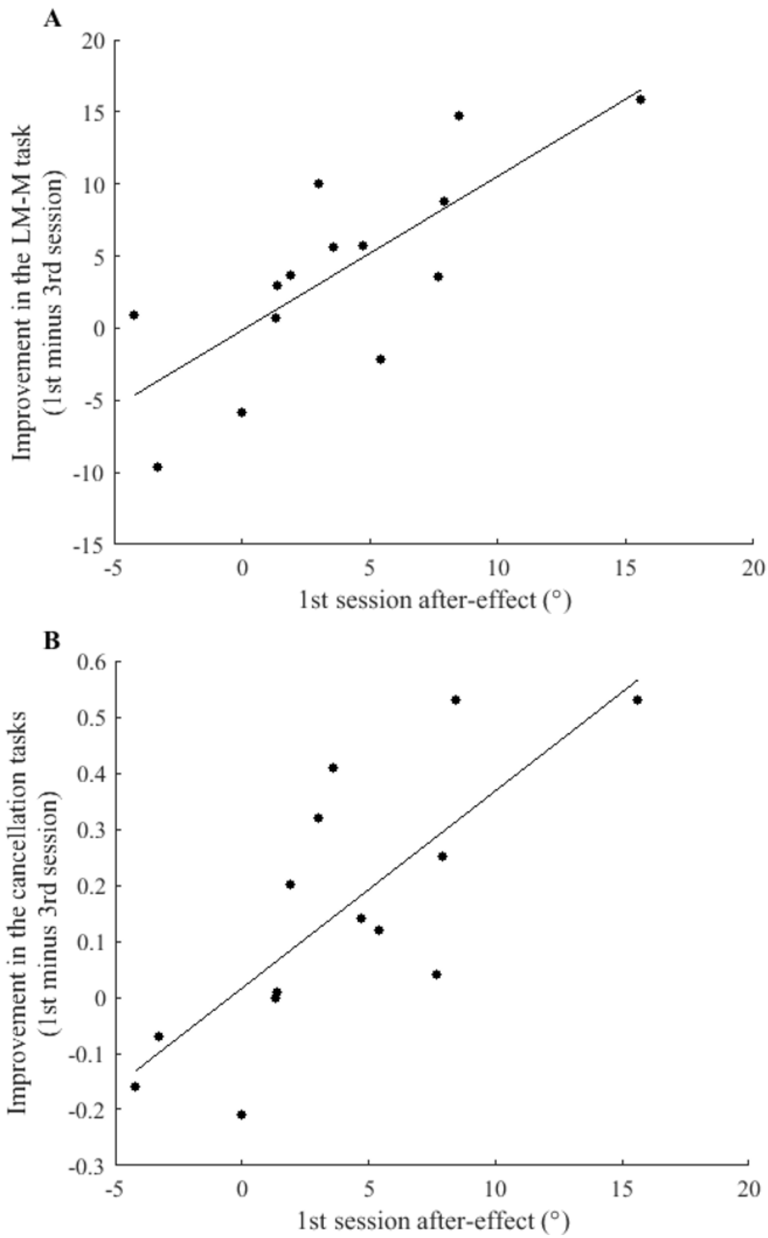

Figure 6. Improvement at follow up in the LM-M task (A) and the cancellation tasks (B) plotted against the magnitude of the proprioceptive after-effect in the first session.

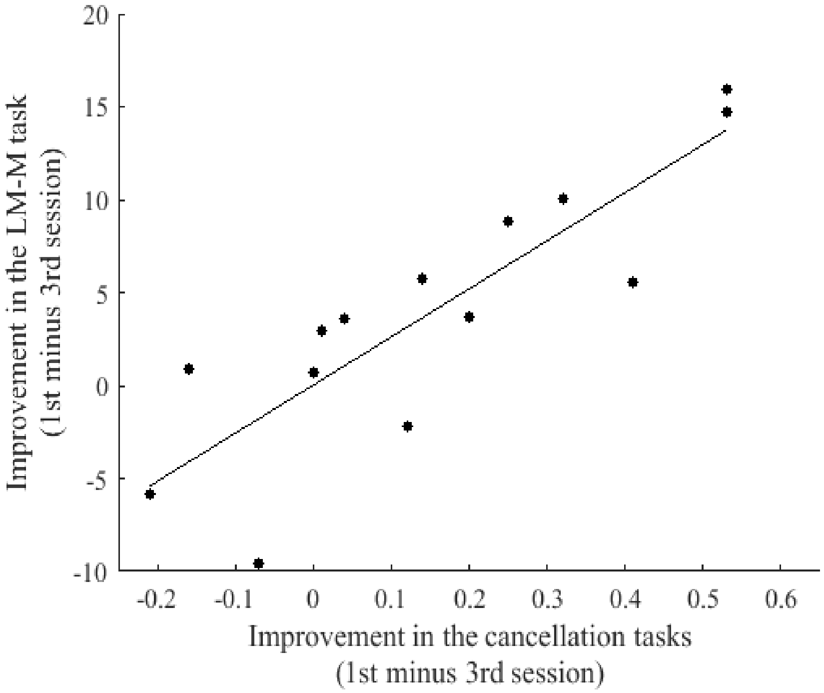

Figure 7. Improvement in the LM-M task (baseline minus follow-up, y-axis) plotted against the improvement in the cancellation tasks (baseline minus follow-up, x-axis).

Brain lesions observed in patients with higher vs. lower improvement in motor related tasks at follow-up session

Based on the median splits calculated for the improvement in performance at follow-up session in the LM-M and in the cancellation tasks, patients were consistently classified into groups with higher vs lower improvement. To identify the brain regions that were predominantly involved in patients showing a low prism-related improvement in motor related tasks, we subtracted the superimposed lesions of patients with a higher improvement (n = 7; Figure 8, bottom panel) from those of patients with a lower improvement (n = 7; Figure 8, top panel). As indicated in Figure 8, an extended area could be defined were lesions were 57% more common in patients showing a lower performance improvement in motor related tasks. This area included the right inferior and middle temporal gyri, thalamus, angular and supramarginal gyri, postcentral gyrus, fusiform gyrus, and hippocampus. As for the opposite subtraction, brain regions including the right superior temporal gyrus, temporal pole, heschl gyrus, and superior, middle and inferior frontal gyri were damaged 57% more often in patients with higher performance improvement in motor related tasks. Additionally, a higher percentage of overlap was observed in the insula, the putamen and the rolandic operculum (71%) (Figure 9)[1].

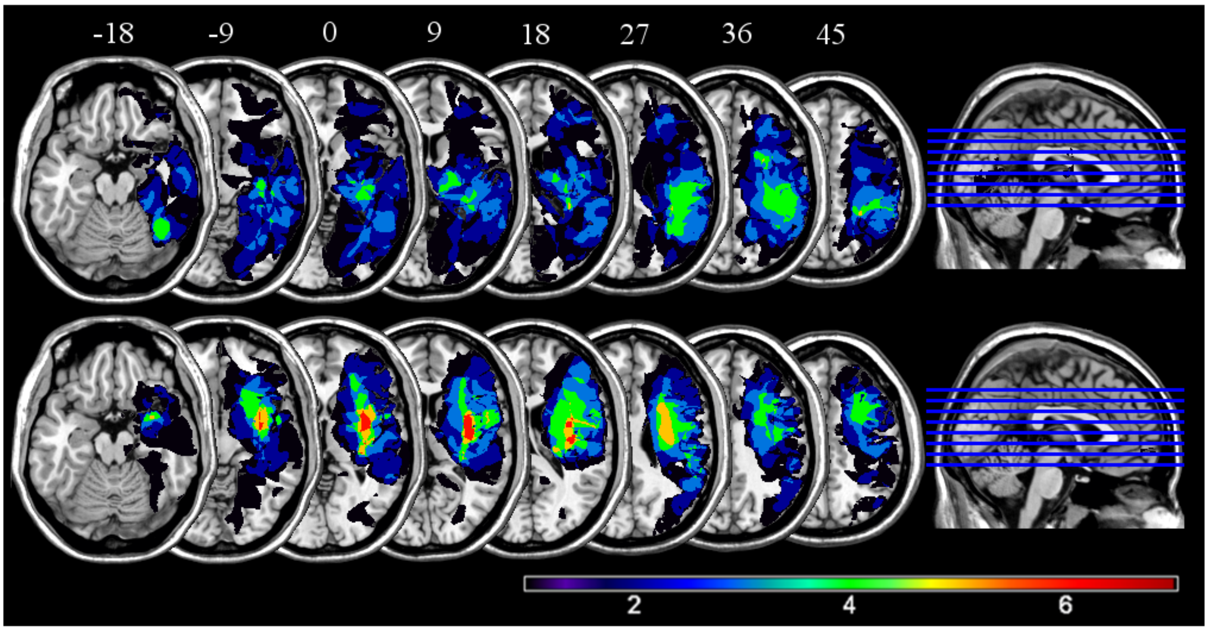

Figure 8. Overlay lesion plots of patients with low (top panel; *n* = 7) and with high improvement in motor related tasks (bottom panel; *n* = 7). The number of overlapping lesions is illustrated by colors coding increasing frequencies from violet (*n* = 1) to red (*n* = 7). The MNI *z*-coordinates of the axial sections are given.

[1] In an attempt to provide statistical evidence for the subtraction data, binary voxel-based lesion-symptom mapping analyses (VLSM) were conducted by means of the Liebermeister test. As for the uncorrected statistical maps ($p < .05$), the results obtained resembled those of the maximal subtraction lesion overlaps. However, when narrowing the analyses to voxels damaged in at least 1 patient and applying FDR correction none of the results remained significant. This could be explained by the small size of the patients' sample. It has been suggested that a large number of observations (minimum 20) is required to survive multiple comparison correction (Timmann et al., 2009).

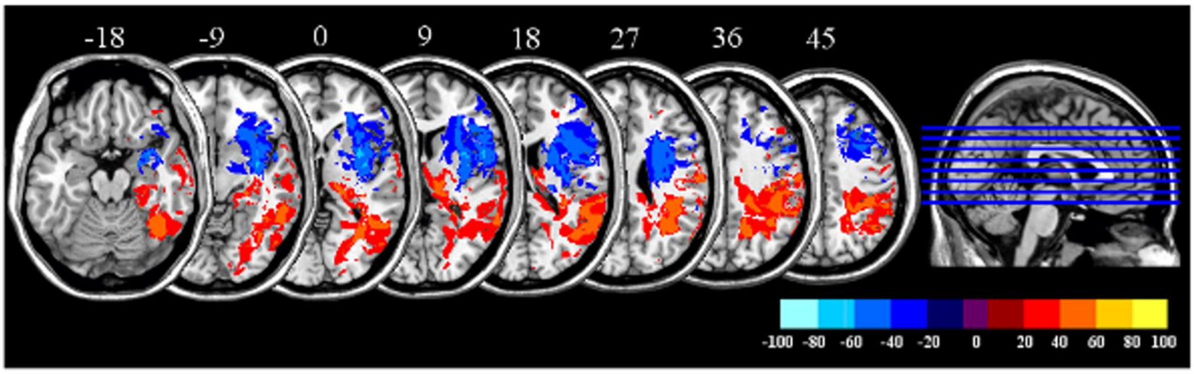

Figure 9. Overlay plots of the subtracted superimposed lesions of patients with high minus those of patients with strong improvement in motor related tasks. The percentage of overlapping lesions after subtraction is illustrated by colors coding increasing frequencies from dark red (difference +1) to yellow (difference +7). The different colors from dark blue (difference -1) to light blue (difference -7) indicate regions damaged more frequently in patients with high improvement in motor related tasks as compared to those with low improvement. The MNI *z*-coordinates of the axial sections are given.

Discussion

The present study aimed to shed light on some of the controversies surrounding the neuroanatomical and behavioral aspects related to PA's effectiveness in the treatment of neglect. To this purpose, a study combining neuropsychological and lesion mapping approaches was conducted on a group of neglect patients who underwent a two-week PA protocol consisting of two sessions of intervention and one session of follow-up assessment.

It was found that two-sessions of PA intervention conducted in the same week led to an improvement in neuropsychological performance from the baseline up to the follow-up session conducted one week later. Such an improvement, being positively correlated with the magnitude of the proprioceptive after-effect in the two sessions of prism adaptation, was evident in the LM-M as well as in the cancellation tasks. Furthermore, brain lesions observed in patients showing a low improvement in motor-related tasks and in those showing a high improvement involved parieto-temporal and frontal-subcortical areas, respectively.

The magnitude of the proprioceptive after-effect and its relation with the performance's improvement in motor related tasks

As revealed by the results of the correlation analyses, the magnitude of the proprioceptive after-effect observed in two sessions of prism adaptation showed a significant positive association with the improvement in performance from the baseline up to the follow-up session in the LM-M task and in the cancellation tasks. However, no correlation was detected between the improvement in the LM-V task and the magnitude of the proprioceptive after-effect. In other words, patients who exhibited the strongest proprioceptive response to PA achieved a greater reduction of rightward biases in motor related tasks, and vice versa. This explains the fact that only the two tasks that required *planning and executing movements* toward the left side showed a prism related improvement, whereas the task regarded as entirely perceptual showed none. This finding agrees with the study by Sarri et al., (2008), which likewise reported an association between the magnitude of the proprioceptive after-effect and patients' improvement in neglect tests. Therefore, it could be proposed that the magnitude of the proprioceptive after-effect might serve as a special indicator of the therapeutic potential of prism adaptation. Although there are studies reporting no correlation between the after-effect and the improvement in neglect symptoms (Frassinetti et al., 2002; Pisella et al., 2002), it should be noted that there are some methodological aspects which differentiate them from our study and might therefore account for the discrepancy. For instance, the study by Frassinetti et al., (2002) used the total shift parameter to measure the after-effect whereas we used the proprioceptive parameter to do so. With regard to the employment of the total shift, there is indication that it might not be a reliable measure since it does not seem to distinguish the performance of patients' from that of healthy controls (Sarri et al., 2008). As to the study by Pisella et al., (2002), although they also used the proprioceptive parameter to measure the after-effect, our sample size and analysis approach differed significantly from theirs (two patients, single case analyses).

On the other hand, our finding that the cognitive improvement associated with PA mainly occurred in motor related tasks adds to the results of recent studies suggesting that this therapy method primarily influences motor-intentional performance (Chen et al., 2014; Striemer & Danckert, 2010; Striemer et al., 2016). Such a differential association of PA with motor and perceptual tasks is in line with the results reported by Striemer & Danckert, (2010). They observed that after one session of PA, patients with neglect were significantly less biased to the right in the line bisection task, but showed no change in their performance on a verbal variant of the landmark task (see also Striemer, Russell, & Nath, (2016) for healthy subjects). It should be noted that the LM-M task used by us is comparable to the line bisection task employed by the authors. The only difference is that in our task the lines were kept pre-bisected to assure their perceptual equivalence with the verbal variant of the task. Likewise, the LM-V task here used is essentially analogous to the perceptual landmark task employed by the authors. Although the respective task instructions differed (judge if the bisection mark is closer to the left or to the right side of the line vs. judge if the transection mark is at the center of the line), both performances reflect the same underlying perceptual bias. However, there is one methodological shortcoming of our study that should be considered when interpreting patients' performance on the LM-V task. In contrast to the manual version, in which patients could freely mark any point along the entire line, the verbal version limited their response choices to nine possible locations. Therefore, the latter task was probably less sensitive and informative to estimate the position of the subjective straight-ahead, which could also explain that no significant improvement could be herewith demonstrated.

Different treatment protocols and measures of the after-effect might account for the prism-related improvement in non-motor related tasks

Even thought our study seems to support the idea that prism adaptation has a stronger impact on the motor components of neglect, it is important to consider that other studies do not fully agree and suggest that the influence of prism adaptation is rather broad (Jacquin-Courtois et al., 2013; Newport & Schenk, 2012; Serino, Bonifazi, Pierfederici, & Làdavas, 2007). When looking at possible reasons behind such discrepancies among studies, it is worth taking into account two main elements namely, the intensity of the treatment protocols and the parameter chosen to quantify the after-effect. Interestingly, in contrast to studies suggesting a more extended influence of prism adaptation on spatial cognition those studies in favor of a predominant influence on motor performance tended to conduct less intensive treatment protocols and to quantify the after-effect with the proprioceptive shift (Chen et al., 2014; Striemer & Borza, 2017; Striemer & Danckert, 2010; Striemer et al., 2016). Therefore, it might be speculated that in order to detect beneficial effects not only in motor-related but also in perceptual tasks one would need, on the one hand, to perform more intensive and longer protocols of prism adaptation and, on the other hand, to use additional parameters to quantify the after-effect. The speculation about the frequency and duration of the treatment is in agreement with a recent study suggesting that patients showing perceptual-attentional deficits of neglect might require more sessions of prism adaptation than those with motor-intentional deficits to experience a beneficial effect (Goedert, Zhang, & Barrett, 2015).

On the other hand, the speculation regarding the after-effect's parameter is in consonance with the study by Rode et al., (2015) which reported that patients' improvement on the Behavioral Inattention Test (BIT) over a period of six months showed a strong correlation with the changes in the visual shift parameter during the same period (Rode et al., 2015). Along these lines, the improvement in the LM-V task would have possibly shown a significant correlation with the effects of prism adaptation if the visual shift parameter of the after-effect had been measured and included in the correlation too. This poses an interesting question for future studies, which should further examine whether the strength of the visual shift might relate to any long-term improvement in perceptual tasks.

The beneficial cognitive effects of prism adaptation seem to develop over time

A second important finding of our study is that the prism-related improvement was exclusively observed in the follow-up session. Such an incremental character of the beneficial cognitive effects associated with PA has been previously acknowledged by some studies (Hatada, Miall, & Rossetti, 2006; Humphreys, Watelet, & Riddoch, 2006; Pisella, Rode, Farnè, Tilikete, & Rossetti, 2006; Rossetti et al., 1998). They have indicated that, consistent with an underlying process of plastic adaptation, these effects tend to develop and to become stronger over time. This would be in line with the idea that the beneficial cognitive effects of prism adaptation lag behind the lower-level after-effects (Pisella et al., 2006).

The integrity of temporal and inferior parietal regions might contribute to prism-related improvement in motor related tasks

As indicated by the results of the subtraction analyses, those patients who showed a lower improvement in motor related tasks had lesions involving temporal (middle and inferior gyri), and inferior parietal (supramarginal and angular gyri) areas. These finding is in agreement with a lesion study suggesting that lesions affecting middle temporal and posterior parietal areas, among others, tend to be predominant in patients showing minimal or no benefit from PA in tests assessing egocentric neglect (Gossmann et al., 2013). It should be noted that, since the center of the lines was always aligned with the mid-sagittal axis of the patient's body, the LM-M task might have had, similar to the cancellation tasks, the characteristics of an egocentric task. The contribution of right temporal areas to PA-related improvement has also been indicated by another VLSM study which reported lesions sparing the right temporal lobe in patients profiting from this intervention (Chen et al., 2014).

Frontal and subcortical lesions might facilitate the prism-related improvement in motor related tasks

As compared to patients who showed a lower improvement in perceptual tasks with motor involvement, those whose improvement was higher had extensive lesions in frontal areas. Although the presence of greater proprioceptive (O'Shea, Pastor, Pisella, & Rossetti, 2009; Rossetti et al., 1998) and total (Farne et al., 2002) after-effects has often been attributed to posterior parietal lesions, recent evidence has pointed to the possible contribution of frontal damage (Chen et al., 2014; Gossmann et al., 2013). For the interpretation of this finding it might be relevant to consider the positive role that unawareness could play in the success of PA intervention (Jacquin-Courtois et al., 2013; Rode et al., 2015; Rossetti et al., 2015). Previous studies looking at the emotional responses of patients during PA have reported that when exposed to visual shifting prisms they do not show the level of galvanic skin response (GSR) that normal subjects would show in the same situation (Rode et al., 2015; Rossetti et al., 2015). The authors have interpreted such a GSR suppression as a lack of awareness and proposed it as a convenient mechanism, which might have prevented and/or delayed the cognitive compensation of the optical shift. On the basis of this evidence, it would be reasonable to consider that the damage of frontal areas, known as affecting executive functions, might further reduce the possibility to engage an explicit compensation strategy, therefore resulting in an increased sensorimotor adaptation.

Furthermore, the evidence that patients who showed a higher improvement in motor related tasks had extensive damage in frontal areas is compatible with the idea that the proprioceptive component of the after-effect might be specially facilitated by the presence of frontal lesions. Conversely, it might be speculated that patients showing a higher prism-related improvement in perceptual tasks without motor involvement might tend to exhibit a stronger visual shift and to have more posteriorly located lesions. Notwithstanding, taking into account that we did not measure the visual parameter of the after-effect and that the lesion analyses were rather descriptive, these results should be interpreted carefully. Moreover, since no correlation was established between the improvement at follow-up in the LM-V task and any measure of the after-effect, it might be questionable to attribute such an improvement to the specific effect of prism adaptation.

Finally, the areas affected in patients showing a higher improvement in motor related tasks are somewhat similar to the neuroanatomical correlates of premotor or intentional neglect.

A number of studies have reported that anterior lesions, mainly frontal and subcortical, are associated with the presence of motor intentional neglect deficits affecting the execution of contralateral aiming movements (Ghacibeh, Shenker, Winter, Triggs, & Heilman, 2007; Husain, Mattingley, Rorden, Kennard, & Driver, 2000; Sapir, Kaplan, He, & Corbetta, 2007). Curiously, some studies have indicated that patients whose symptoms correspond with a motor-intentional neglect type seem to profit more from PA therapy (e.g. Fortis, Goedert, et al., 2011; Goedert et al., 2013). Based on this evidence, our results might support the idea that there is a relationship between the presence of frontal and subcortical lesions and the manifestation of PA-related improvement, especially in motor related tasks.

Concluding remarks

The present study evidenced that the magnitude of the proprioceptive after-effect measured during two weekly sessions of prism adaptation was positively correlated with the improvement until the following week (follow-up session) in two perceptual tasks requiring motor responses. This finding suggested that patients' potential to show a prism-related improvement in motor related tasks might be indicated by the strength of their proprioceptive response (proprioceptive after-effect). Moreover, in line with an underlying process of plastic adaptation, such an improvement was not immediately observed, but seemed to develop over time. As to the neuroanatomical basis of this relationship, the results of the subtraction analyses suggested that patients' improvement in perceptual tasks with high motor involvement might be facilitated by the integrity of temporo-parietal areas and the damage of frontal and subcortical areas.

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5 General Discussion

5.1 Right middle and angular gyri contribute differently to directional motor deficits

The study of the DMD associated with left unilateral neglect has been marked by an ongoing debate as to whether and to what degree right frontal and parietal lesions might contribute to their occurrence. Study 1 of this thesis intended to elucidate the neuroanatomical basis of DMD, by further examining the involvement of rAG and rMFG in the planning and execution of contralateral movements. To this end, rTMS was delivered to these areas while participants performed a pointing task toward two laterally located targets. It was found that applying rTMS to the posterior part of rAG, adjacent to the caudal intraparietal sulcus, delayed the initiation of movements directed toward the contralateral target. Interestingly, this effect applied to internally guided movements (IGM) but not to externally guided ones, therefore suggesting that the selection of contralateral movements was particularly disrupted. It should be noted that in contrast to other TMS studies, which have remarked the role of the intraparietal sulcus in planning (Davare, Zénon, Pourtois, Desmurget, & Olivier, 2012; Marco Davare, Zénon, Desmurget, & Olivier, 2015; Koch, Fernandez, Olmo, Cheeran, & Schippling, 2008) contralateral movements regardless of the visual goal, the effect reported here clearly pertained to the goal of the action. Therefore, this finding allows speculating that the supposed preference of inferior parietal areas toward contralateral movements (Battaglia-Mayer, Mascaro, Brunamonti, & Caminiti, 2005) might involve not only advanced stages of movement planning closer to the implementation of the motor program, but also more abstract and cognitive stages related to decision making.

Along these lines, it might be considered that, depending on the timing and on the location parameters used to stimulate the angular gyrus and adjacent areas along the intraparietal sulcus, distinct aspects associated with the planning of contralateral movements might be differentially affected. Whereas stimulating medial intraparietal areas shortly before movement onset might impair the computation of the reaching vector (Davare et al., 2012), stimulating caudal intraparietal areas concurrently with the presentation of the starting cue might interfere with the selection of the movement (Gutierrez-Herrera, Saevarsson, Huber, Hermsdörfer, & Stadler, 2017). Interestingly, there is recent evidence that the posterior part of the right intraparietal sulcus is indeed involved in action selection (Ariani, Wurm, & Lingnau, 2015).

As to the stimulation of the rMFG, results did not indicate any signs of directional bradykinesia. They did however point to a curious effect on the completion of IGM performed in the contralateral direction without visual feedback. In conditions where visual feedback was removed at movement onset there was a tendency to redirect leftward movements toward the right side. Considering that this effect was limited to IGM, it might be suggested that the stimulation of the rMFG interfered with the ongoing decision to move toward the left. This interference possibly resulted from the weakening of the value attributed to contralateral movements, which at the same time increased the likelihood of changes of mind upon visual feedback removal. Furthermore, the higher biomechanical costs of leftward movement as compared to rightward ones, together with possible deficits affecting the short-term memory representation of the contralateral target, might have additionally affected the value attributed to contralateral movements.

It is important to remark that the lack of visual feedback seemed to be particularly critical to elicit the redirection of leftward movements. Although such redirecting behavior has not been previously described in patients with neglect, it does bear some resemblance to reports of patients showing a reduced exploration of the left side of space while blindfolded (Cubelli, Nichelli, Bonito, De Tanti, & Inzaghi, 1991; Mesulam, 1981). These exploration deficits, being mainly associated with frontal lesions, have been regarded as rightward biases with a predominant motoric nature. On the basis of this evidence, it might be speculated that the redirection of leftward movements was a manifestation of rightward motor biases which in this case happened during movement execution since this was the earliest point at which blindfolding occurred. Perhaps an earlier effect possibly related to the initial movement decision would have been observed if blindfolding had occurred prior to movement onset. However, it should be noted that the stimulation of the rMFG did not completely prevent contralateral movements from happening. Participants were still capable of completing some of them although visual feedback was not provided during movement execution. Considering this indication, it might be speculated that depending on the extension and chronicity of the underlying lesion, the execution of leftward movements might be more or less impaired. Whereas a patient with an extensive frontal lesion might be consistently reluctant to direct movements toward the contralateral side (directional akinesia), a healthy subject with a transient lesion induced by TMS might occasionally avoid executing contralateral movements under particularly demanding conditions, for instance when performing IGM without visual feedback. Nevertheless, this remains pure speculation and further investigation is needed to explore whether the absence of visual feedback is a contributing or rather a decisive factor in eliciting directional motor deficits associated with right middle frontal lesions.

Taken together, the effects induced by both stimulation conditions point to interesting differences between the roles of right middle frontal and caudal intraparietal areas in contralateral aiming movement. Whereas the former appears to be involved in the implementation of the motor program intended to explore the contralateral side of space, the latter seems to be concerned with the cognitive aspects of movement planning in the contralateral direction. In line with this idea, lesions affecting both areas seem to contribute to directional motor deficits in different ways. Lesions of right caudal intraparietal areas, on the one hand, appear to cause an unbalanced competition between rightward and leftward motor programs, thus biasing movement selection toward the ipsilateral hemispace and increasing reaction times of leftward aiming movements. This idea is in agreement with the evidence that patients with lesions in right inferior parietal areas show a pathologically strong interaction between posterior parietal and primary motor areas of the left hemisphere, which might reinforce the rivalry between rightward and leftward motor programs (Koch, Oliveri, et al., 2008). Lesions of right middle frontal areas, on the other hand, seem to decrease the likelihood of executing and/or carrying on contralateral movements, especially in conditions where visual feedback of the target is not available. Such a reluctance to move in the contralateral direction might be explained by a disruption of the motor mechanisms necessary to manually explore the contralateral side of space (Mesulam, 1981).

5.2 The proprioceptive after-effects of prism adaptation might influence the directional motor aspects of neglect

Although the beneficial effects of PA on unilateral neglect are seemingly recognized, there is little consensus on whether they might extend equally to perceptual and motor aspects of neglect. Study 2 of this thesis intended to further examine the differential influence of PA on these two aspects. To that end, 19 neglect patients were treated during one week with two separate sessions of PA. In addition, three perceptual tasks with varying degrees of motor involvement were used to assess patients' neuropsychological performance at three time points, namely, at baseline, after the second session, and 7 to 8 days after the first session (follow-up session). In line with previous studies suggesting an association between the size of the prism's after-effect and the extent of neglect amelioration (Farne et al., 2002; Sarri et al., 2008), it was found that the magnitude of the proprioceptive after-effect in the first session was significantly correlated with an improvement in performance from the baseline to the follow-up session in the LM-M task and in the cancellation tasks. Interestingly, no correlation was detected between the improvement in the LM-V task and the magnitude of the proprioceptive after-effect. These findings are in line with the idea that prism adaptation is particularly effective in improving motor exploration (Chen et al., 2014) and planning (Striemer & Borza, 2017) toward the contralateral side of space. Furthermore, they provide further evidence to the suggestion that prism's related improvement applies to tasks requiring a response with the adapted hand as opposed to purely perceptual tasks (Striemer, Russell, & Nath, 2016).

Nevertheless, although the results of this study add to the assumption that PA has a predominant impact on the motor components of neglect, it is important to consider that other studies do not fully agree and suggest that the influence of PA is rather broad (Jacquin-Courtois et al., 2013; Newport & Schenk, 2012; Serino et al., 2007). Two possible reasons dealing with methodological aspects might account for the discrepancies among studies, namely the intensity of the treatment protocol and the parameter chosen to quantify the strength of the after-effect. Interestingly, in contrast to studies suggesting a more extended influence of prism adaptation on spatial cognition those studies in favor of a predominant influence on motor performance tended to conduct less intensive treatment protocols and to quantify the after-effect with the proprioceptive shift (Chen et al., 2014; Striemer & Borza, 2017; Striemer & Danckert, 2010; Striemer et al., 2016). Therefore, it might be speculated that in order to detect beneficial effects not only in motor-related but also in perceptual tasks one would need, on the one hand, to perform more intensive and longer protocols of prism adaptation and, on the other hand, to use additional parameters to quantify the after-effect. As for the latter speculation, it should be noted that a recent study by Rode (2015) reported that patients' improvement on the Behavioral Inattention Test (BIT) over a period of six months showed a strong correlation with the changes in the visual after-effect during the same period. Along these lines, the improvement in the LM-V task observed in study 2 would have possibly shown a significant correlation with the effects of prism adaptation if the visual shift parameter of the after-effect had been measured and included in the correlation too. Taking this into consideration, it might be reasonable to suggest that the proprioceptive after-effect is associated with the prism-related improvement in motor related tasks whereas the visual after-effect does it with the improvement in perceptual tasks.

5.3 Patients' response to prism adaptation might be facilitated by the preservation of temporo-parietal areas together with the damage of basal ganglia and frontal areas

Studies have increasingly suggested that the presence of certain brain lesion patterns might facilitate patients' ability to respond effectively to prism adaptation. Notwithstanding, diverse findings have been reported to date, thus making it difficult to determine the neuroanatomical basis of prism-related improvement. Study 2 of this thesis aimed to differentiate the lesion patterns of patients showing low vs high improvement in neuropsychological performance following two weekly sessions of prism adaptation. Subtraction analyses indicated that lesions involving temporal (middle and inferior gyri), and inferior parietal (supramarginal and angular gyri) areas were predominant in patients who showed a lower improvement in motor related tasks, whereas those patients whose improvement was larger had lesions mainly involving frontal and subcortical areas. On the basis of these findings, it might be speculated that the presence of lesions sparing posterior areas and affecting frontal and subcortical ones could predispose patients to show strong proprioceptive responses to prism adaptation and therefore to perform better in perceptual tasks with motor involvement.

It should be noted that the idea that prism adaptation relies on the preserved function of posterior brain areas has been generally supported in the literature (Luauté et al., 2006; Sarri et al., 2008; Serino et al., 2006). The contributing role of frontal (Chen et al., 2014) and subcortical lesions (Gossmann et al., 2013), on the contrary, has been suggested until recently and no convincing explanation has been offered so far to explain it. A possible explanation for the positive influence of frontal lesions on the response to prism adaptation might be inferred from recent studies examining the benefits of being unaware of the optical shift induced by prisms. These studies claim that such an unawareness prevent patients from engaging a cognitive strategy and correspondingly increases the strength and the duration of the after-effect (G. Rode et al., 2015; Rossetti et al., 2015). Based on this evidence, it is speculated that the presence of frontal lesions might have further interfered with cognitive control processes, thus enhancing the proprioceptive adaptation response and increasing the chances of neuropsychological improvement in motor related tasks.

An alternative explanation which could account for the positive effects of frontal and basal ganglia lesions is derived from the study by Mattingley, Bradshaw, Bradshaw, & Nettleton, (1994). The authors reported that, compared to patients with parietal lesions, patients with frontal and subcortical lesions tend to recover faster from directional motor deficits. In line with their interpretation, it might be suggested that in case of frontal and subcortical damage, PA might be more likely to activate adequate residual functions or compensating mechanisms. In other words, whereas the role of posterior areas in PA might be more specialized and difficult to compensate for, frontal areas might rather have a more general and executive role which could be more easily restored.

5.4 Shortcomings and future directions

Considering that the two research studies included in this thesis employed novel protocols and tasks to examine the neuroanatomical underpinnings and rehabilitation of DMD, some methodological shortcomings should be noted. The current section outlines the most critical shortcomings of each study and provides suggestions for future investigations

With respect to study 1 two main shortcomings were identified. The first one pertains to the timing of the stimulation protocol. Taking into account that the TMS stimulation was delivered in sequences of six pulses which started simultaneously with the presentation of the cue, it is uncertain whether the interference effect extended into the execution of the movement. Although in some trials, especially in those involving externally guided movements, the pulses extended shortly into movement onset, the influence of the stimulation on movement execution was most probably insufficient and irregular. In line with these observations, a more appropriate way to assess DMD using TMS would be to distribute the pulses evenly between planning and execution phases. For instance, one alternative approach would be to separate both phases artificially, by instructing participants to start planning the movement and to withhold movement execution until a second cue is presented. Thereby, single pulses can be delivered within each movement phase separately. Additionally, since the effects of the stimulation were limited to internally guided movements, it is highly possible that the first two pulses were more effective than the rest to influence contralateral movement and consequently, only the early stages of movement planning akin to movement selection and decision making were affected. Taking this into account, a suggestion for future studies would be to employ either shorter sequences of pulses or single-pulse protocols. This would not only facilitate the interpretation of the findings but would also enable a more precise examination of directional motor deficits.

The second shortcoming identified in study 1 has to do with how visual feedback was manipulated in the experiment. Although removing visual feedback at movement onset was convenient to test for the presence of planning and programming deficits induced by the stimulation, an additional condition preventing visual feedback before movement onset would have been useful to confirm the presence of motor deficits affecting the spontaneous exploration of the contralateral side of space. Considering that, the lack of visual feedback seemed to be crucial to bring out rightward motor bias associated with rMFG's stimulation, future studies should try to replicate this finding and further explore whether removing visual feedback at an earlier stage could induce comparable movement biases.

As to the second study, two main shortcomings were identified. The first one refers to the employment of pre-bisected lines in the motor version of the landmark task. Although the intention behind it was to make this version as perceptually comparable as possible to the verbal version of the task, it is likely that the pre-existing mark contaminated the motor execution and increased the perceptual difficulty of the task. It should be noted that although patients' improvement in this task still appeared to be influenced by prism adaptation, future studies should preferably use standard line bisection tasks without pre-bisected lines in order to get a cleaner picture of the influence of prism adaptation on motor performance.

The second shortcoming of study 2 relates to the fact that, due to logistical reasons, no control group was used. However, this was partially overcome by using correlation analyses, which allowed assessing patients' improvement relative to the strength of their adaptation response. In other words, the control criterion was not whether patients exposed to the intervention improved more than patients who were not exposed, but whether patients' improvement was modulated by their amount of responsiveness to the intervention. Nevertheless, future studies adopting a similar approach should use larger sample sizes than the one used here. This would help to examine whether the observed correlation is stable. Besides, using a larger sample would be advantageous to conduct statistically more powerful analysis on the lesion data.

5.5 Conclusion

This doctoral thesis provides a novel understanding of the participation of right middle frontal and angular lesions in the directional motor aspects of neglect. Unlike previous studies attributing DMD to either frontal or parietal lesions alone, this thesis offers compelling evidence that both of them are likely to affect different aspects of contralateral aiming movement: right angular lesions slow down the selection of contralateral movements, whereas right middle frontal lesions decrease the likelihood of completing them, especially in conditions where visual feedback of the target is not available. Likewise, these findings suggest that directional motor deficits might not only involve advanced stages of movement planning closer to the implementation of the motor program, but also more abstract and cognitive stages related to decision making.

On the other hand, this thesis indicates that the strength of the proprioceptive response displayed by patients with neglect after PA might relate to their potential improvement in perceptual tasks involving motor performance. Moreover, it suggests that the presence of brain lesions sparing posterior areas and affecting frontal and subcortical ones might contribute to the effectiveness of this intervention.

It should be noted that the findings of this thesis consistently point to the direct and determinant role of right inferior parietal areas in DMD and PA. The corresponding role of frontal areas seems to be rather indirect and remains open to different interpretations. Taking this into consideration, it becomes relevant to further explore the effect of right frontal lesions in the initiation of contralateral movements and their potential contribution to prism-related improvement. One aspect that would be particularly worth examining is whether the role of frontal areas in contralateral aiming movement is mainly executive and related to response production.

Overall, this thesis expands our knowledge of the neuroanatomical basis of DMD and provides us with useful evidence to implement more effective and solid intervention protocols of PA.

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List of publications

Gutierrez-Herrera, M., Eger, S., Keller, I., Hermsdörfer, J., Saevarsson, S. (in press). Neuroanatomical and behavioral factors associated with the effectiveness of two weekly sessions of prism adaptation in the treatment of unilateral neglect. *Neuropsychological Rehabilitation*.

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Eidesstattliche Versicherung /Affidavit

Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertation "Neuroanatomy and Rehabilitation of the Directional Motor Deficits associated with Unilateral Neglect" selbstständig angefertigt habe, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

I hereby confirm that the dissertation "Neuroanatomy and Rehabilitation of the Directional Motor Deficits associated with Unilateral Neglect" is the result of my own work and that I have only used sources or materials listed and specified in the dissertation.

Munich, 19 March 2018 Maria Gutierrez-Herrera

Declaration of Author Contributions

Chapter 2

Authors: *Styrmir Saevarsson; Simone Eger; Maria Gutierrez-Herrera;*

The author of this thesis is a co-author of the opinion article; S.S. formulated the topic and focus of the article; S.S., M.G.-H and S.E wrote the article.

Chapter 3

Authors: *Maria Gutierrez-Herrera, Styrmir Saevarsson, Thomas Huber, Joachim Hermsdörfer, Waltraud Stadler*

The author of this thesis shares the first authorship of the manuscript with Styrmir Saevarsson; S.S. conceived and designed the study, with the help of J.H, W.S and M.G.-H; M.G.-H conducted the MRI acquisition and pre-processed the images under the supervision of T.H and W.S; M.G.-H. implemented and performed the experiment; M.G.-H conducted data analyses; M.G.-H, W.S and S.S wrote the manuscript; J.H. provided critical feedback on the manuscript, which was further commented by T.H.

Chapter 4

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The author of this thesis is the first author of the manuscript; S.S. conceived, designed, and supervised the study; S.S, M.G.-H., and S.E. recruited patients and conducted the study protocol; M.G.-H. and S.S contributed equally to data' analysis, results' interpretation, and manuscript's writing; J.H. provided critical feedback on the manuscript, which was further commented by I.K. and S.E.

Munich, 19 March 2018

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