

# The role of eye position signals in spatial cognition

PhD thesis

by

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## ***I. Abstract***

My PhD dissertation investigates the role of the eye position signals in visual localization and visuospatial attention. Visual localization can be defined as the ability to find the exact position of an object in sight relative to the body. It is used in daily life for instance to reach to a cup or to match a voice with an unknown face in a crowd. Because our eyes can rotate in the orbits, visual targets at different locations around the body can project at the same retinal site. Therefore, information about eye position is essential for correct visual localization. This information can derive from two main signals: the corollary discharge, which is a copy of the oculomotor command, and eye proprioception, which is the afferent signal from extraocular muscles. The literature about which signal is used in visual localization is controversial. It is not clear whether the signals are combined and if yes, what the principles that underlie their combination are.

Visuospatial attention is the process by which locations are selected for a privileged access to neural processing resources. The brain implements attention using priority maps. The “value” on the priority map is higher for locations where important objects are or can appear. Body-centered priority maps, just like the body-centered object maps must incorporate eye position information. The source of the gaze information in the priority maps is unknown and could, in principle be different from that in the object maps.

This thesis gives an overview of the findings presented in four papers. I manipulated the proprioceptive eye position signal in the somatosensory cortex and measured effects on behavior.

The results suggest that the corollary discharge and eye proprioception are weighted flexibly, depending on task demands. Visual localization for action, i.e. pointing, depends on the fast corollary discharge, while eye proprioception plays a role for visual localization for perception, i.e. cross-modal spatial attention.

## ***II. List of Papers in chronological order***

**Paper 1.** Daniela Balslev, Marc Himmelbach, Hans-Otto Karnath, Svenja Borchers & Bartholomäus Odoj (2012). *Eye proprioception used for visual localization only if in conflict with the oculomotor plan.* **J Neurosci**, 32(25), 8569-8573.

**Paper 2.** Bartholomäus Odoj & Daniela Balslev (2013). *Visual sensitivity shifts with perceived eye position.* **J Cogn Neurosci**, 25(7), 1180-1189.

**Paper 3.** Daniela Balslev, Bartholomäus Odoj, & Hans-Otto Karnath (2013). *Role of somatosensory cortex in visuospatial attention.* **J Neurosci**, 33(46), 18311-18318.

**Paper 4.** Bartholomäus Odoj & Daniela Balslev (2016). *Role of oculoproprioception in coding the locus of attention.* **J Cogn Neurosci**, 28(3), 517-528.

### ***III. Background***

#### **1. The role of eye position signals in visual localization**

##### **1.1 Visual localization requires information about eye position**

When our eyes rotate in the orbits, visual objects can create the same image on the retina, despite being at different locations around the body. To extract visual location for object-directed action, eye position information must be integrated with retinal information.

In the early 20th century, two main hypotheses about the source of eye position information for visual localization were stated. Eye position information was proposed to derive from 1.) the corollary discharge (CD), a copy of the oculomotor command (von Helmholtz, 1925), also called the outflow hypothesis, or to be 2.) an eye proprioceptive signal, deriving from proprioceptors (Sherrington, 1918) located in the extraocular muscles (EOM), also called the inflow hypothesis. The eye position signal is then incorporated in the eye position estimate.

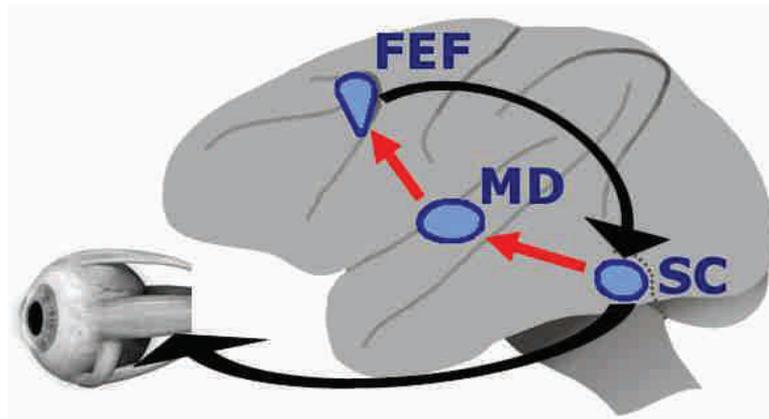
These two hypotheses have been extensively investigated in the last century. Despite this effort, the results seem contradictory and the source of the eye position signal remains incompletely understood. In the following paragraphs I will review these studies. I will discuss the evidence for and against each hypothesis and propose a solution to the apparent contradiction in previous experimental results.

## 1.2 The CD as a potential source of eye position information

### *Pathways of the CD*

The corollary discharge is a copy of the oculomotor command. The oculomotor command is issued in the frontal eye field (FEF), streams down to the superior colliculus (SC) and from there it reaches the motor nuclei in the brain stem, which drive the eye muscles (Figure 1). In the SC a copy of this oculomotor command, the CD is generated. The CD is then transmitted to the mediodorsal thalamus (MD). From there it returns to the FEF, the brain region where the original eye movement was initiated (Sommer & Wurtz, 2004b). Physiologically, this pathway was demonstrated using single cell recordings (Sommer & Wurtz, 2004a). Disruption of the CD pathway by injecting muscimol, affected only double-step saccades, where the movement trajectory must be recalculated by taking eye position into account, but not single-step saccades, whose planning does not require knowledge of eye position (Sommer & Wurtz, 2004b).

Further electrophysiological experiments have shown that the SC-MD-FEF pathway is not unique. A second ascending projection leads from the SC via the pulvinar to the lateral intraparietal area and extrastriate visual areas, like the MT (middle temporal) (Sommer & Wurtz, 2003).



**Figure 1. Schematic pathway for the oculomotor command and the corollary discharge.** The oculomotor command is generated in the frontal eye fields (FEF) travels to the superior colliculus (SC) before reaching the extraocular muscles (black arrows). In the SC, a copy of the oculomotor command streams over the mediodorsal thalamus (MD) back to the FEF (red arrows). Adapted from Sommer and Wurtz (2008).

### ***Empirical support for the role of CD in visual localization***

Can the information contributed by the CD provide an accurate estimate of eye position? Studies in monkeys, whose eye muscle were deafferented by a bilateral section of the trigeminal nerves, show that the loss of eye proprioception does not reduce accuracy or precision of hand (Lewis, Gaymard, & Tamargo, 1998) or eye movements to visual targets (Guthrie, Porter, & Sparks, 1983), when these movements are performed without visual feedback. These results lead to the hypothesis that the corollary discharge is sufficient and eye proprioception is not needed in visual localization. Further, subjects are not able to feel the amount or direction of a passively rotated eye (Brindley & Merton, 1960), suggesting that proprioception may not be able to provide position information at all.

The suggested redundancy of eye proprioception for visual localization could be explained by the fact, that our eyes, unlike our limbs, move very fast in a relatively predictive environment. They rest on the orbit floor, coated in connective tissue and are very unlikely to be exposed to sudden mechanical perturbations. Therefore, the evolution of predictive neural mechanisms like the CD, that allow precise and fast control of position, would make the slower, proprioceptive feedback obsolete.

However, motor predictions can be wrong. This can for instance occur during growth or after surgery, when the anatomy of the orbit changes. Therefore some authors have proposed that eye proprioception calibrates CD in the long-term. Studies in strabismus patients after surgery suggest that this recalibration is completed after 2-3 days (Lewis et al., 1998; Steinbach, 1986). Only after this time, pointing accuracy reached its peak and remained constant.

However, acute perturbations, e.g. after rubbing the eyes, require the capacity to update the prediction. Otherwise the error would accumulate after each passive perturbation. Therefore a solely role for CD as eye position signal remains under debatable.

### ***Further Functions of the CD***

By arriving at the FEF briefly before saccade onset, the corollary discharge can provide a fast estimate of future eye position before the eye actually moves. This is important, since our eyes move very fast and the feedback of sensory information about eye position falls victim to delays due to receptor dynamics and conduction

time (Franklin & Wolpert, 2011). A predictive gaze position estimate, incorporated in a feedforward model for motor control (Wolpert & Miall, 1996), counteracts these delays. Additionally, it is able to compensate for the noise in the sensory feedback (Franklin & Wolpert, 2011).

Further, an eye position input is critical for a stable visual perception, despite continuously moving retinal images (Sommer & Wurtz, 2008). A disrupted eye position signal (CD or proprioception) can result in a misperception of motion induced by eye movements. During smooth-pursuit eye movements, a patient with bilateral extrastriate cortex lesions, including the visual area MT, perceived motion of the stationary world at the same velocity of his eye movement. It was assumed that the lesion in MT lead to disrupted eye position information. Due to this lack of CD or eye proprioceptive information, the patient was unable to take own eye movements into account to cancel out consequent retinal movement. Instead he perceived the retinal slip as external movement (Haarmeier, Thier, Reppow, & Petersen, 1997).

### **1.3 Eye Proprioception as a potential source of eye position information**

In contrast to Brindley and Merton (1960), Skavenski showed that humans after all are aware of the direction of passive eye rotation in total darkness, despite a lack of retinal information or a CD (Skavenski, 1972). He argues that the psychological method of subjective reports, used in these Brindley's and Merton's experiments (1960) are inadequate to detect a sense of eye position, compared to the forced choice procedure used in Skavenski's experiments (1972). Another reason for the different findings may be the fact that the proprioceptive eye position signal is very subtle and could easily go unnoticed by inexperienced subjects, like those tested by Brindley and Merton.

This awareness can only be explained by afferent eye position signals from the extraocular muscles. While the authors agree about the existence of this afferent eye proprioceptive signal, its receptors, its pathway into the central nerve system (CNS) and its role are heatedly debated.

### ***Possible proprioceptive receptors***

In skeletal muscles the main proprioceptors are muscle spindles, activated by muscle stretch, and Golgi tendon organs (GTOs), activated by tendon stretch during muscle contraction. The presence of muscle spindles in the EOM, however, is not consistent over species. For instance these receptors are not present in the macaques. Human muscle spindles in the body of the EOM (Cooper, Daniel, & Whitteridge, 1955) show an abnormal morphology (Donaldson, 2000). It is therefore unclear whether they are functional or not. Alternatively, palisade endings at the musculotendinous junctions of the EOM, which are common to most investigated species (Richmond, Johnston, Baker, & Steinbach, 1984), could play a role as EOM proprioceptors. However, these structures have a striking similarity with the motor end plates - they stain for acetylcholine, have their cell body close to oculomotor nuclei and possess a molecular phenotype that share many immunohistological features with the motor end plate (Zimmermann et al., 2013). This suggests that palisade endings are at least partly motor structures, although they show also sensory features (Lienbacher, Mustari, Hess, Buttner-Ennever, & Horn, 2011). Their supposed role as specialized tendon organs (Richmond et al., 1984), their partly sensory morphology (Lienbacher et al., 2011) and proof from strabismus patients propose that palisade endings indeed are probable to carry proprioceptive information. Indeed, behavioral studies show that strabismus patients are more disturbed in open-loop pointing after a marginal myotomy in the musculotendinous regions, compared to a recession, where the tendon was cut, due to a greater disruption of palisade endings (Steinbach, Kirshner, & Arstikaitis, 1987).

So although the access of the CNS to eye proprioceptive information is beyond doubt, the question, whether muscle spindles, palisade endings or both are the proprioceptive receptors is still open to debate.

### ***Ascending pathways of the eye proprioceptive signal***

In cats and monkeys EOM proprioceptors are innervated by ipsilateral neurons of the ganglion of the trigeminal nerve (Porter, Guthrie, & Sparks, 1983). It is assumed that this sensory innervation is also present in humans. However, an afferent stretch response of the EOM was found in the oculomotor nuclei in the brain stem (Buisseret, 1995) and the superior colliculus (Abrahams & Rose, 1975; Donaldson &

Long, 1980) in humans. The processing of ocular proprioceptive information in these predominantly motor structures is surprising for a sensory modality. This unusual overlap in the structures that process the oculomotor command/CD and proprioception could suggest the functional interaction between the sensory and motor signals.

### ***Cortical projections of the eye proprioceptive signal***

Cortical proprioceptive signals reach the visual (Buisseret & Maffei, 1977) and the frontal cortex (Dubrovsky & Barbas, 1977).

More recently, Wang and colleagues were able to map the primary projection of the eye proprioceptive signal in area 3a of the monkey somatosensory cortex (Wang, Zhang, Cohen, & Goldberg, 2007). They found that in this region, each neuron is tuned for one radial direction of gaze. The more the eye was rotated to this preferred direction, the higher the firing rate of the neuron (Figure 2A). To prove that this eye position signal is proprioceptive and to rule out the possibility that it derives from the corollary discharge, Wang and colleagues applied a local anesthetic in the orbit. This resulted in a paralysis of the eye. The position signal in the contralateral area 3a was abolished during the period of the block and returned when the anesthesia wore off.

In humans, Balslev and Miall found an eye proprioceptive projection in the anterior parietal cortex using TMS (Balslev & Miall, 2008). Neuronavigation confirmed that the area targeted by TMS is located in the postcentral gyrus (Balslev, Siebner, Paulson, & Kassuba, 2012). A study, using functional magnetic resonance imaging (fMRI) showed a proprioceptive projection from the eye muscles in the somatosensory cortex (Balslev, Albert, & Miall, 2011). I will refer to this area targeted by TMS as  $S1_{EYE}$ . Balslev and colleagues (2008) found that a decrease of the excitability of the left  $S1_{EYE}$  due to repetitive transcranial magnetic stimulation (rTMS) causes an underestimation of the rotation of the eye in the orbit and reduces the ability to correctly assess the effect of passive movement applied to the eyeball.

### ***Eye proprioception and visual localization***

Contrary to some studies that deny eye proprioception a role in visual localization, other studies show clear visual localization errors after manipulating with this signal.

First, patients with a disease of the trigeminal nerve (Campos, Chiesi, & Bolzani, 1986) show a significant error in locating a light source in darkness, when viewing with the involved eye compared to the contralateral, normal eye.

Second, a change in monocular visual localization can be achieved by a passive deviation of the non-viewing eye (Gauthier, Nommay, & Vercher, 1990). For this purpose a suction lens is secured to the cornea of the non-viewing eye through a light air vacuum produced by a syringe. Then the subject turns the gaze at 30° and the eye is fixed in this position. When participants view targets monocularly, while their non-viewing eye is passively rotated, their reaching movements overshoot the targets in the direction of the eye rotation. Thus, a proprioceptive manipulation in the absence of an eye movement and hence a motor command and CD cause localization errors (Gauthier et al., 1990).

Third, mechanical vibration to EOM, a maneuver known to stimulate muscle spindles and cause illusory sensation of eye rotation, affects the accuracy of saccades to targets that are no longer in sight (Allin, Velay, & Bouquerel, 1996; Lennerstrand, Tian, & Han, 1997). Finally, rTMS over the left S1<sub>EYE</sub> cause an underestimation of the rotation of the eye in the orbit (Balslev & Miall, 2008). These studies suggest that eye proprioception contributes to the eye position estimate used in visual localization.

### ***Further functions of the eye proprioceptive signal***

In cats, eye muscle proprioception is needed for the development of normal depth perception (Graves, Trotter, & Fregnac, 1987). Other studies also assign this sensory modality a role in long-term maintenance of ocular alignment (Gauthier, Vercher, & Blouin, 1995) and sensing of visual target velocity with respect to the head (Donaldson & Knox, 1993; Gauthier et al., 1995)

## **1.4 Controversy about the role of CD and eye proprioception for visual localization**

The findings presented in the previous section suggest a role of eye proprioception in visual localization. This stands in direct contrast with those studies which indicate that CD is a sufficient and eye proprioception redundant (Guthrie et al., 1983; Joiner, Cavanaugh, Fitzgibbon, & Wurtz, 2013; Lewis et al., 1998).

How could these contradictory findings be explained? Firstly, the different results arise from studies in different species (monkeys vs. humans) with known differences in the eye proprioceptive signal (e.g. macaques do not have muscle spindles in the EOM, only palisade endings; Donaldson, 2000). Thus interspecies differences could be responsible for the apparent contradiction. Secondly, despite a bilateral section of the trigeminal nerves (Guthrie et al., 1983; Lewis et al., 1998), still sufficient proprioceptive input from palisade endings could reach the CNS via the oculomotor nuclei (Lienbacher et al., 2011) to perform accurate visual pointing (Lewis et al., 1998) or saccades to visual targets (Guthrie et al., 1983).

### **1.5 Can the model of a weighted average of both eye position signals explain these controversies?**

In the skeletal system, both proprioception and the efference copy of the motor command contribute to limb localization (Wolpert, Ghahramani, & Jordan, 1995). Perhaps in the ocular system a combination of both eye position signals too is used to generate the eye position estimate.

The current model for signal combination is precision-based optimization, where each signal is weighted according to its variance (Ernst & Bulthoff, 2004; van Beers, Sittig, & Gon, 1999). In a cross-modal, visual-haptic discrimination task, for example, where participants determine the taller of two bars that are simultaneously seen and felt, participants rely more on visual information. However, when changing the reliability of the visual stimulus by introducing image noise, the weight of the haptic information increases (Ernst & Banks, 2002). Such weighting of sensory signals can also be found between other modalities, like vision-audition and vision-proprioreception (Ernst & Bulthoff, 2004).

Similar to cross-modal integration, some studies suggest that eye position information arises from a weighted average between eye proprioception and the CD. The weight for eye proprioception has been calculated to be ~ 26-32% (Bridgeman & Stark, 1991; Gauthier et al., 1990). These values were calculated by comparing the errors in open-loop pointing and perception of straight ahead before and after manipulating eye proprioception. However, the hypothesis of a weighted average still cannot account for the findings of Lewis and colleagues (Lewis et al., 1998). Indeed, if eye proprioception contributed to the multimodal estimate in order to increase the preci-

sion of this estimate, then one would expect that in its absence, the precision of the eye position estimate would decrease. This was not the case in the experiment by Lewis et al. (1998).

## **1.6 The search for a reconciling hypothesis**

In this thesis I investigated whether the brain uses the available eye position signals flexibly, depending on task demands. This would explain the inconsistencies in current literature. According to this hypothesis, under some circumstances CD can be used exclusively as eye position signal, while other circumstances can lead to a weighted average of both eye position signals, the CD and eye proprioception. I will argue for this new idea of a flexible integration later in this thesis.

## **2. The role of eye position signals in visuospatial attention**

### **2.1 Visuospatial attention**

#### *The definition of visuospatial attention*

Only a small amount of the visual information on the retina can be processed further towards perception and action. Stimuli considered unimportant are ignored and only information deemed relevant to further behavior is processed. This prioritization defines attention.

The selection mechanism can be modulated by stimulus saliency (bottom-up, stimulus-driven or exogenous attention). Subjects detect bright and colorful target stimuli faster than colorless (Duncan, 1989). Also selection mechanisms can be controlled by task-related goals (top-down, voluntary or endogenous attention). Subjects are better at detecting an object in a visual scene when they have feature information, such as its location or color, in advance (Corbetta & Shulman, 2002).

### *Different models for visuospatial attention*

An established way of thinking about attention is a mental spotlight, which illuminates/selects information from a constrained region in visual space. This is the zoom-lens model of spatial attention (Eriksen & Hoffman, 1973; Posner, 1980). Over the last two decades, further models of selective attention, with focus on the mechanisms of selection, emerged. At some point, between input and response, objects in the visual input compete for representation, analysis, or control (Desimone & Duncan, 1995). Desimone and Duncan (1995) propose a model, where 'attention is an emergent property of many neural mechanisms working to resolve competition for visual processing and control of behavior'. They note that, top-down and bottom up mechanisms bias this competition.

### *The model of priority maps*

One model to describe this competition of stimuli across the visual space is the salience map, proposed by Koch and colleagues (Itti & Koch, 2000; Walther & Koch, 2006). In this theoretical model, a salience map is created, based on bottom-up inputs. The inputs are filtered by several feature detection filters. Then a salience map is created, which codes the importance of each location. Locations on the map with the highest salience are allocated the highest priority in accessing neural processing resources.

In this thesis, I use the model of priority maps (Bisley & Goldberg, 2010), a version of the salience map model. Priority maps combine top-down and bottom-up signals so that the value at a location on the map scales with the importance of the object that is or may appear in the world at that location.

The native format of the priority maps is retinotopic – see Golomb 2008 J Neurosci. This means that the priority map is overwritten for each eye movement.

To stabilize the focus of attention across eye movements or to allow cross-modal interactions in spatial attention, the retinotopic priority map must be updated after each eye movement or transformed into a more stable object or body-centered reference frame. Both these processes require eye position information. The source of the eye position signal is unknown.

## 2.2 Eye position signals and visuospatial attention

### *Eye position modulates the allocation of attention*

A number of studies have shown a link between the ocular and spatial attention systems. For example, planned eye movements to visual targets involuntarily increase the target's detectability (Deubel & Schneider, 1996). Furthermore, stimulation of the oculomotor structures such as FEF or the SC not only evokes saccades (Bruce, Goldberg, Bushnell, & Stanton, 1985; Robinson, 1972) but can also create a bias in visual sensitivity (Cavanaugh & Wurtz, 2004; Ruff et al., 2006). Not only eye movement, but also eye position affect visuospatial attention. For instance, Craighero and colleagues (Craighero, Nascimben, & Fadiga, 2004) have shown that eye position can modulate visuospatial attention in a Posner paradigm. When the screen was centered 40° to the left/right of subjects sagittal plane, attentional benefits for stimuli appearing in subjects' temporal spatial hemifield decayed, even if the retinal stimulation was identical as in the classical paradigm without eye rotation. They interpreted the results in favor of the 'premotor theory of attention' (Rizzolatti, Riggio, Dascola, & Umiltà, 1987). This theory postulates a strict link between covert orienting of attention and the programming of explicit ocular movements and predicts a perceptual enhancement for orienting attention from the preparation of a saccadic eye movement towards the to-be-attended location. In the '40°-condition' of Craighero's experiment, the eye was kept at an extreme position in the orbit. This position limited the execution of a saccade to the temporal hemifield, whereas it allowed saccades to the nasal hemifield. This motor limitation leads to faster reaction times in the nasal hemifield.

Another example is the perceptual advantage for sounds presented nearer the direction of gaze (Pavani, Ladavas, & Driver, 2005).

### *Eye proprioception could be integrated in the priority maps*

The source of eye position signals in the priority maps is currently unknown. Priority maps can update predictively (Pertzov, Zohary, & Avidan, 2010), which points to the CD as the eye position signal. In other experiments however, the updating of priority maps can show a latency of 100-200 ms (Golomb, Chun, & Mazer, 2008) after an eye movement. In a gaze-contingent behavioral paradigm, Golomb and colleagues (2008) presented a memory cue to subjects near to a fixation point. After a

saccade, a probe was presented within different time delays either at a position, retinotopically or spatiotopically identical to the memory cue. The experiment showed that immediately after a saccade, attention is primarily maintained at the previous relevant retinotopic coordinates of the cue. After 100-200 ms, however, the task-relevant spatiotopic coordinates dominate.

This latency is compatible with the time it takes the eye proprioceptive signal to reach the cerebral cortex (Xu, Wang, Peck, & Goldberg, 2011). Further, a study about an eye position signal that modulates neuronal activity in the lateral intraparietal (LIP)(Andersen & Mountcastle, 1983), an area associated with spatial attention, showed a time delay of 150 ms to adapt the firing rate to a new gaze position (B. Y. Xu, Karachi, & Goldberg, 2012). Again, this time delay coincides with the latencies of the eye proprioceptive signal. Although there could be many reasons for the delay in updating the retinotopic priority map, this time frame leaves open the possibility that, at least in some circumstances, the priority maps need the eye proprioceptive signal.

### **2.3 Hypothesis: Does S1<sub>EYE</sub> play a role in spatial attention ?**

Previous research has associated visuospatial attention with a network in the higher-order frontal, parietal and temporal cortices and some subcortical structures such as the thalamus and SC (Bisley & Goldberg, 2010; Karnath & Rorden, 2012; Petersen & Posner, 2012). This network has so far not included S1.

Such a role can however be presumed. Balslev and colleagues show that a manipulation of S1<sub>EYE</sub>, using transcranial magnetic stimulation (TMS) leads to a change in visual sensitivity (Balslev, Gowen, & Miall, 2011). In a cued letter discrimination task, Balslev and colleagues presented targets equidistant from a lateral fixation point before and after S1<sub>EYE</sub>-TMS. They found a bias for targets presented closer to the eye orbit center after S1<sub>EYE</sub>-TMS. They assumed that this attentional shift was congruent with a shift in perceived eye position. However, this assumption was never tested. Here, I test this assumption of spatial congruency between the shift of visuospatial attention and perceived eye position after S1<sub>EYE</sub>-cTBS to clarify S1<sub>EYE</sub>'s role in the visuospatial attention network. In an attempt to replicate these findings using a different way of altering the eye proprioceptive signal, I test a patient with a lesion in

S1<sub>EYE</sub>. Unlike previous methods, this allowed me to investigate the long term effect of manipulated eye proprioception on visuospatial attention. Finally, I perform experiments in which attention was indexed by the pattern of exploratory eye movements in a visual search task.

## ***IV. Methods***

### **1. Established ways to manipulate eye proprioception signals**

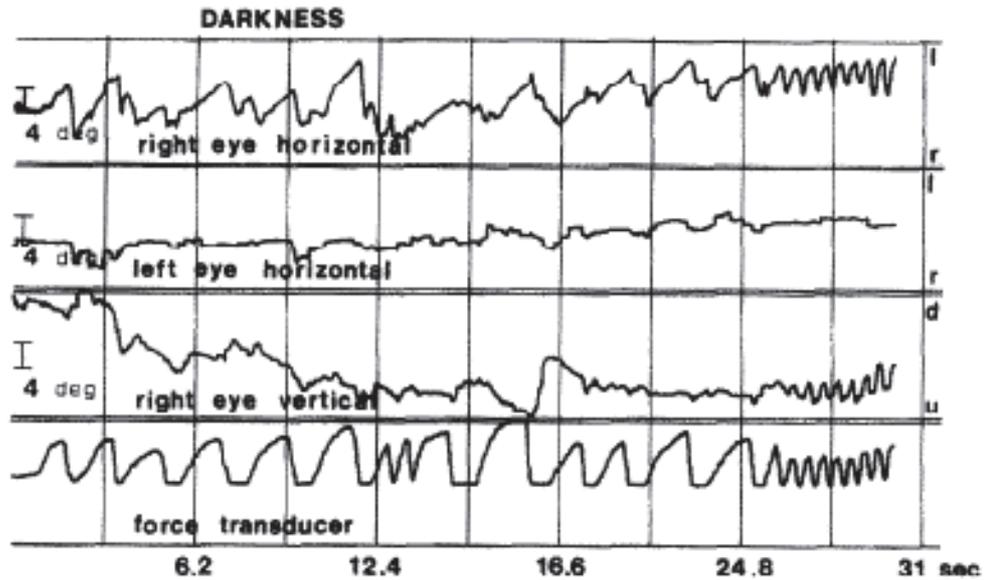
In the previous chapter, different ways to manipulate eye proprioception have been mentioned. Here I want to sum up the different established methods, discuss their advantages and disadvantages, and present and justify the methods I used in my thesis.

#### **1.1 Section of the trigeminal nerves**

The most direct way to manipulate the eye proprioceptive signals is the deafferentation of the eye muscles by a bilateral section of the trigeminal nerves (Guthrie et al., 1983; Lewis et al., 1998). However, this method has clear disadvantages. First, because it is invasive, it cannot be applied humans. Given the interspecies differences in the anatomy of the eye proprioceptive system, experiments in non-human animals may not be that informative about the function of this modality in humans. Second, one can never be sure that the eye proprioceptive input has been cut completely, since eye proprioceptive information could be carried through other connections than the trigeminal nerve (Gentle & Ruskell, 1997), ie through the oculomotor nerves.

#### **1.2 Passive eye deviation/ brief push of the eye**

Disturbed eye proprioception can also be achieved by the appliance of external force, either by a passive rotation of the non-viewing eye, e.g. after mounting a scleral lens (Gauthier et al., 1990), or after a brief push of the non-fixating eye, for instance in darkness or when the eye is closed. In both cases, the eye has been moved without an oculomotor command and hence without a CD. Only eye proprioception is manipulated (Figure 2).



**Figure 2. Eye movements in darkness with (first row) and without (second row) brief pushes (from (Ilg, Bridgeman, & Hoffmann, 1989)).** During frequent pushes of the right eye (last row) over time in darkness, the right eye rotates horizontally to the left (first row), in direction of the applied force. The left eye does not rotate (second row).

The CD can be manipulated by a sustained press of the viewing eye during fixation. Pushing the viewing eye triggers an oculomotor command to maintain fixation in the presence of the external force. During this maneuver, thus there is a CD but no proprioceptive inflow (Bridgeman & Stark, 1991). This approach is an elegant way to test the contribution of both eye position signals. It was used, among others, to define the weight for eye proprioception (Bridgeman & Stark, 1991; Gauthier et al., 1990).

There are however disadvantages. First, it is a very unusual, non-physiological kind of stimulation. Second, passive eye deviation requires the presence of an ophthalmology consultant for safety reasons. Third, we can only analyze the result of an acute mismatch between eye proprioception and the CD after each push. We have no possibility to see the effect of a long-term mismatch. Finally, the amount of stimulation, at least in the push condition is very difficult to control. Since the push is performed normally in total darkness by the subject herself or himself, the experimenter cannot control the force or direction applied.

### **1.3 Transcranial magnetic stimulation (TMS) for assessing the role of the cortical eye position signals**

#### ***Continuous Theta Burst Stimulation (cTBS)***

Transcranial magnetic stimulation (TMS) is a non-invasive method to stimulate neural pathways in the brain of conscious subjects through the intact scalp. The underlying principle is Faraday's law of electromagnetic induction. A rapidly changing magnetic field induces an electric current in the brain. This induced current leads to a depolarization or hyperpolarization of neural axons (Barker, Jalinous, & Freeston, 1985). The focality and depth of the stimulation is bound to biophysical limitations and depends on coil type and size, the tissue distribution it passes (e.g. scalp, skull, cerebrospinal fluid and cortex) and each tissue's conductivity (T. Wagner, Rushmore, Eden, & Valero-Cabre, 2009). According to these biophysical constraints, the magnetic field decays rapidly with the distance from the coil (Pell, Roth, & Zangen, 2011). Studies which use computational models, neuroimaging, EEG/MEG and behavior analysis suggest that TMS activates cortical neurons up to 2.5 cm beneath the scalp. Further it is possible to distinguish stimulation effects of brain sites ~1.5 cm apart and from scalp positions only 0.5-1cm apart (Brasil-Neto, McShane, Fuhr, Hallett, & Cohen, 1992; Heller & van Hulsteyn, 1992; Roth, Amir, Levkovitz, & Zangen, 2007; Schluter, Rushworth, Mills, & Passingham, 1999; T. A. Wagner, Zahn, Grodzinsky, & Pascual-Leone, 2004).

In repetitive TMS (rTMS), seconds to minutes of stimulation over a target brain area changes cortical excitability for minutes to hours after the TMS train (Pell et al., 2011; Robertson, Theoret, & Pascual-Leone, 2003; Thut & Pascual-Leone, 2010). This change in excitability can lead to long-term potentiation (LTP) or long-term depression (LTD), assessed as increases and respectively decreases of the amplitude of a neuron population response to electrical stimulation (Esser et al., 2006). Whether a stimulation leads to an increase or a decrease of excitability depends on the stimulation protocol (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005).

Recent studies show that the effect of TMS also depends on the initial state of the affected system. By systematically manipulating neural activation states, like adaptation for a stimulus attribute, before application of TMS one can selectively target specific neural populations within the affected region (Cattaneo, Sandrini, &

Schwarzbach, 2010; Silvanto, Muggleton, & Walsh, 2008). This method, called TMS adaptation (TMSA), predicts that TMS improves processing of the adapted attributes and decreases performance for non-adapted attributes. However, the underlying mechanisms of this relatively new method are still under debate (Dayan, Censor, Buch, Sandrini, & Cohen, 2013).

One of the most efficient repetitive stimulation protocol to achieve a LTD effect is continuous theta burst stimulation (cTBS). This stimulation type has shown a very constant and long-lasting (~ 60 min) decrease of excitability in the human motor cortex (Huang et al., 2005). Huang and colleagues used the size of the electromyographic (EMG) response in the first dorsal interosseous (FDI) muscle, triggered by single pulse TMS as an objective measure for the excitability of the primary motor cortex. These motor evoked responses (MEPs) were measured before and after 40 seconds of cTBS over the primary motor cortex. Up to 60 minutes after cTBS the MEPs were significantly lower compared to baseline measurements. The same protocol applied over the human somatosensory cortex, showed a decrease of the excitability in the human somatosensory cortex for ~ 13 min (Ishikawa et al., 2007). In my experiments I used cTBS to decrease the excitability of human S1<sub>EYE</sub>.

### *Safety issues*

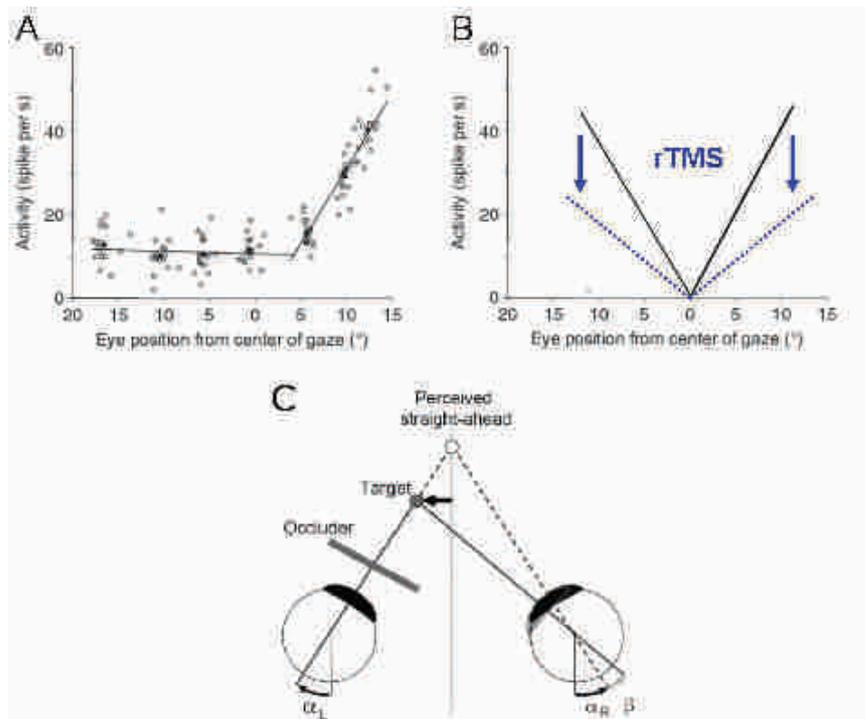
TMS is considered a safe technique, approved by the U.S. Food and Drug Administration (FDA) for clinical use.

However, in some, though very few, cases TMS has had a severe side effect, the occurrence of a seizure (Rossi, Hallett, Rossini, & Pascual-Leone, 2009). For this reason, stimulation must adhere strictly to international safety guidelines (Rossi et al., 2009; Wassermann, 1998). TMS-induced seizures are extremely rare (16 cases in healthy people reported worldwide in the last 20 years). For cTBS there is only one published case where a seizure occurred (Oberman & Pascual-Leone, 2009). Less serious side effects, like mild headache, neck pain or short-time tinnitus have been reported more frequently (~5%).

### *The effect of TMS over S1<sub>EYE</sub>*

Balslev and Miall used inhibitory rTMS over S1 to attenuate the proprioceptive input from the extraocular muscles. They hypothesized that the human eye proprioceptive area is organized like its monkey homologue (Wang et al., 2007). That is the larger the eye rotation, the higher the neural activation (Figure 3, A). Because this principle applies for all radial directions, at population level, this firing pattern should be V-shaped (Figure 3, B), with a higher level of activation for larger orbital eccentricities, regardless of direction. They predicted therefore that rTMS over S1<sub>EYE</sub> will cause an underestimation of eye rotation. Balslev and Miall asked participants to locate a visual target relative to the body. Participants navigated an LED in darkness until it felt straight in front of their nose. They found that rTMS over S1<sub>EYE</sub> increased the error in visual localization. In accord with the prediction, a target located ~4 degrees laterally was perceived to be located straight in front of the nose (Figure 3, C). The effect was modulated by passive eye movement. Before rTMS participants had no problem correcting for the proprioceptive perturbation. After rTMS however, a push to the eye shifted perceived eye position in the direction of the push. All effects were specific to stimulation in S1<sub>EYE</sub> and did not occur after stimulation in a control area in the primary motor cortex (M1). This interaction suggests a change in the eye proprioceptive signal after S1<sub>EYE</sub>-rTMS.

According to the assumed organization of S1<sub>EYE</sub>, neural activity raises with the rotation of the eye, so the effect of rTMS is expected to be stronger for large angles of eye rotation. Therefore, most of my experimental setups include target presentations at 10-20° left/right from orbit midline, to ensure cortical activity at the pre-cTBS-conditions.



**Figure 3. rTMS effect on the eye proprioceptive signal.** Single neuron activity raises with eccentricity of the eye towards the neuron's preferred direction. Here: for rotation to the eye (A, from Wang *et al.*, 2007). At population level, a V-shaped function can be assumed, showing higher activity for larger orbital eccentricities, regardless of their direction (B). rTMS over this cortical area should result in a decrease of the excitability of the tissue and therefore in lower activity for the same orbital eccentricity (blue dotted lines and blue arrows in B). According to this assumption, rTMS over the human S1 leads to an underestimation (C from Balslev and Miall 2008,  $\beta$ ) of the rotation of the eye at fixation. This results in a shift of the reported position of a target perceived as straight ahead to the left (C, black arrow).

### ***Limits to interpreting behavioral changes after rTMS***

To prove that a brain area is responsible for a psychological function the experimental design must control for obvious confounds. The stimulation could have a general effect on behavior, unrelated to the specific task, like a general increase/ decrease in vigilance after rTMS. To demonstrate task specificity, a control task needs to be conducted.

Second, the observed effect on behavior could be triggered by the experimental setup itself, and not by actual change in excitability of the target site. For instance, a change in performance after compared to before TMS could merely be the result of

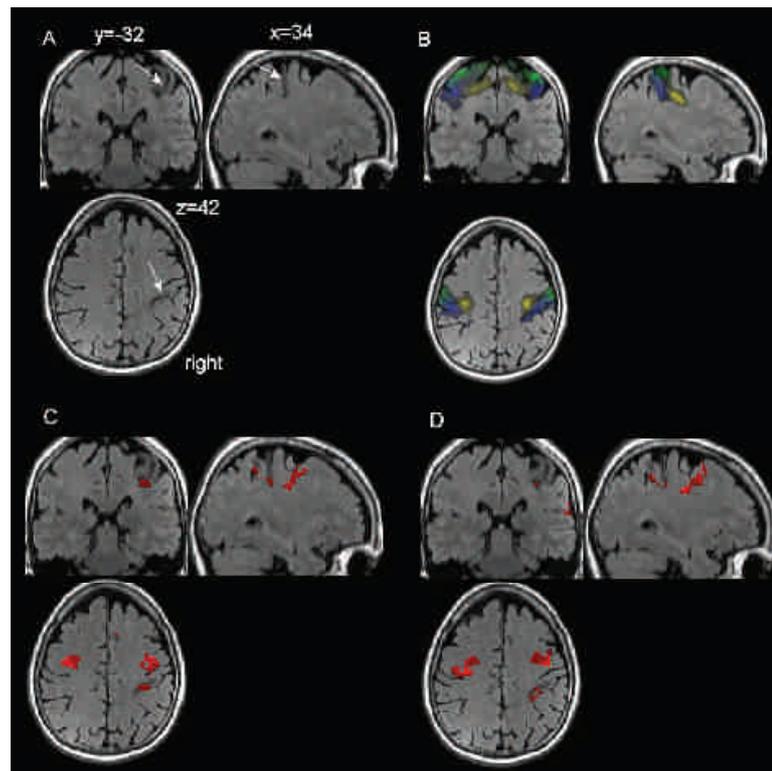
training or a placebo effect. To rule out this confound one can use of a sham coil, a TMS-coil, mimicking an original coil in appearance, sound and effect on the scalp musculature, but not stimulating the brain area. However, most available sham coils do not fulfill these criteria. To address these concerns, one can use active stimulation but at a control site, a brain region where TMS is not expected to have an effect on the task. In most of my experiments I used the motor hotspot in the primary motor cortex (M1). I chose this control area for two reasons. First, the eye is not represented in M1, but rather in the FEF, therefore no effect on eye movements or visual perception should be expected. Second, anatomically, M1 is located closer to critical areas like the FEF and to the eye muscles than the target area  $S1_{EYE}$ . Therefore a possible current spread towards these regions should be more likely for M1- than for  $S1_{EYE}$ -TBS. In some experiments (2, 3 and 4), I used area P3 (after the International 10-20 system for EEG placement) as control area. Hilgetag and colleagues found that repetitive TMS over P3 improves visuospatial attention in the ipsilateral hemifield (Hilgetag, Theoret, & Pascual-Leone, 2001). Therefore I chose this area to control for a possible spread of the induced current from  $S1_{EYE}$  towards P3.

#### **1.4. Neuropsychology for assessing the role of the cortical eye position signals**

Neuropsychology is the oldest method in cognitive neuroscience that allows to study whether a brain area is critical for behavior or cognition. The advantage of neuropsychology, compared to TMS, is the possibility to analyze changes in behavior and cortical reorganization in the long term, years after the lesion. Further, the function of deeper brain layers can be analyzed, while TMS is constrained to regions 1-2 cm under the scalp.

The disadvantage of this method compared to TMS, is that one has no control on lesion size or location. While TMS gives the opportunity to manipulate nearly every superficial brain area with a fair spatial resolution, brain lesions are often diffuse, multiple and rarely restricted to one functional brain area. This makes it more difficult, to ascribe a measured change in behavior to one specific brain region. Further, patients with brain lesions are often more impaired than healthy participants after TMS. They often show reduced vigilance and sensorimotor impairments that must be taken into consideration when preparing a neuropsychological experiment.

In this thesis I used the neuropsychological approach to investigate the effect of a chronic focal lesion in  $S1_{EYE}$  (Figure 4) on visual localization and visuospatial attention. Patient RW's lesion overlapped the projection of eye muscle proprioception in the somatosensory cortex found by Balslev and colleagues using fMRI in healthy participants (Balslev, Albert, et al., 2011). Due to the location of the lesion, a deficit for RW in eye proprioception was presumed and experimentally confirmed. We compared her performance with a group of elderly, healthy controls.



**Figure 4. The lesion of patient RW overlaps with the Brodmann Areas 3a, 1 and 2 and the cortical projection for eye proprioception in the postcentral gyrus.**

The lesion (arrow) is shown in 3 orthogonal projections through the coordinates  $(x, y, z) = (34, -32, 42)$  on a T1-weighted MR-image of the patient's brain normalized to the MNI space (A-D). In panel B, the colour overlays show the probabilistic atlas for area 3a (yellow), 2 (blue) and 1 (green), probabilities 10-100%. The red overlay shows the representation of eye proprioception for the left (C) and the right (D) eye muscles as identified by fMRI in a group of 18 healthy subjects (Balslev, Albert, & Miall, 2011). The threshold for this functional overlay is  $z$ -score  $>2.61$ ,  $p < 0.005$ , uncorrected for multiple comparisons.

## ***V. Research questions***

### **1. Which eye position signals are used for visual localization?**

- Does visual localization require eye proprioception?

I aimed to replicate the results of Balslev et al. (2008) in a neuropsychological study to investigate the role of eye position signals in visual localization in the long term. The motivation for this experiment was the limitations of the TMS method, that only allows to investigate changes in behavior acutely, a few minutes after the “virtual lesion”.

If eye proprioception is incorporated into the eye position signal, we expected our patient with a chronic lesion in the eye proprioceptive area, RW, to be less accurate and precise in locating a visual target in darkness compared to healthy controls. If eye proprioception is not used at all for visual localization, RW was expected to perform undistinguishable from the control group in both conditions.

### **2. Does the contribution of eye position signals to visual localization vary depending on task demands?**

- Does eye proprioception affect the eye position estimate in a cross-modal attention task (visual localization for perception)?
- Does eye proprioception affect visual localization in a visual open-loop pointing task (visual localization for action)?
- Does S1<sub>EYE</sub>-cTBS disturb the felt position of the left index finger without affecting visual pointing accuracy?

The same visual information can be processed differently depending on whether its goal is action or perception (Goodale & Milner, 1992; McIntosh & Schenk, 2009). The shorter response latencies in processing information in the dorsal

stream (Schroeder, Mehta, & Givre, 1998) prompt the hypothesis that spatial representations for action use a eye position estimate optimized for speed. Therefore, the CD as a predictive and very fast information signal, seems to be more suitable than proprioception. In contrast to action, spatial representations for perception may use an estimate that maximizes accuracy. In that case, eye proprioception could be the most suitable eye position signal.

We tested participants in visual localization tasks for reaching (Experiment 2.2) and for cross-modal attention (Experiment 2.1) before and after cTBS over  $S1_{EYE}$ . Under the hypothesis that eye proprioception is more important for perception than for action we expected that  $S1_{EYE}$ -cTBS would have an impact on the locus of attention rather than the reaching end-point.

### **3. Is $S1_{EYE}$ part of the visuospatial attention network?**

- Does cTBS over  $S1_{EYE}$  shift perceived eye position?
- Does  $S1_{EYE}$ -cTBS shift visual sensitivity?
- Does a chronic lesion in  $S1_{EYE}$  affect visual sensitivity?
- Does a lesion in  $S1_{EYE}$  influence exploratory eye movements during visual search?
- Does a coinjury in  $S1_{EYE}$  together with perisylvian lesions have an effect on hemispatial neglect?

A surprising finding in previous studies was that that the eye proprioceptive signal (Balslev, Newman, Knox, 2012) and  $S1_{EYE}$  (Balslev, Gowen, et al., 2011) have a function in visuospatial attention.

If the eye position signal from  $S1$  is incorporated into the priority maps, then the shift in the locus of attention after  $S1$ -rTMS must be spatially congruent with the shift in perceived eye position triggered by  $S1$ -rTMS. Here we investigated this prediction.

Furthermore, we investigated whether a coinjury of  $S1_{EYE}$  together with the neglect-typical perisylvian lesion is associated with a milder neglect (Experiment 8). Patients with a right perisylvian stroke show contralesional neglect, namely a right-

ward bias in spatial attention (Karnath & Rorden, 2012). During visual search, neglect patients prefer to fixate away from midline, in their right, ipsilesional hemispace (H. O. Karnath, 1994; Karnath, Niemeier, & Dichgans, 1998). Because an isolated S1<sub>EYE</sub> lesion leads to a bias in spatial attention towards the midline (Experiments 6.2 and 7), we hypothesized that, when S1<sub>EYE</sub> and the perisylvian network are injured together, the sum of two effects may lead to a milder left-sided neglect. We tested this hypothesis with an voxelwise lesion behavior mapping (VLBM).

In summary, these experiments investigated whether the somatosensory area, via its oculoproprioceptive input, is part of the visuospatial attention network.

## VI. Own Experiments

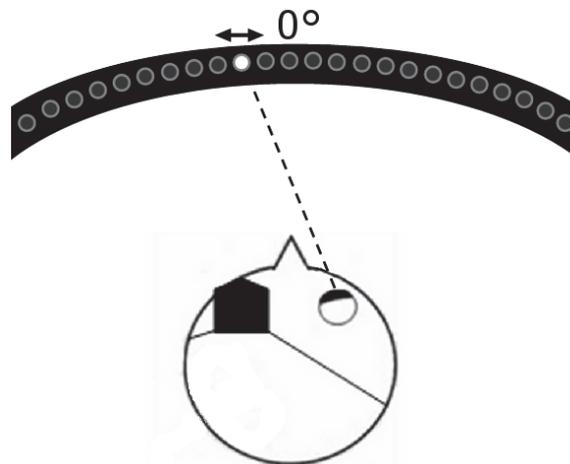
### 1. Eye Position and Visual Localization

#### Experiment 1. - Does visual localization require eye proprioception?

(**Paper 1** - Daniela Balslev, Marc Himmelbach, Hans-Otto Karnath, Svenja Borchers & Bartholomäus Odoj (2012). *Eye proprioception used for visual localization only if in conflict with the oculomotor plan.* **J Neurosci**, 32(25), 8569-8573)

#### Methods

Patient RW and a group of elderly controls performed a visual localization task, similar to the TMS-experiment by Balslev and Miall (1998). They navigated an LED in total darkness until they felt it was located straight in front of the nose (Figure 5). If eye proprioception is incorporated into the eye position signal, we expected RW to be less accurate and precise than the control group.

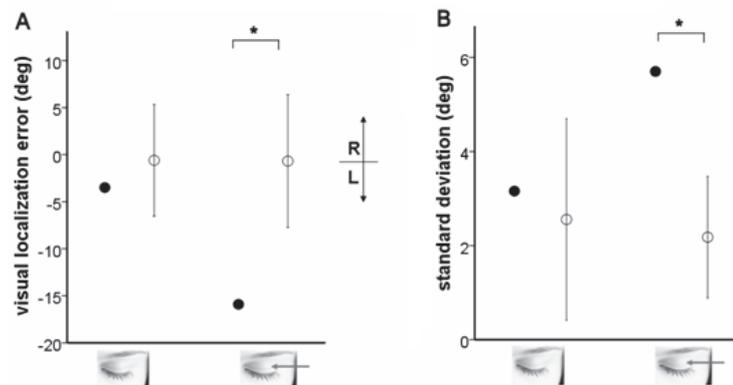


**Figure 5. Setup for experiment 1.** Participants sat head-fixed in darkness with their left eye patched, in front of a LED array, aligned with head/body midline. They navigated a randomly lit LED until they perceived it straight ahead (0°). In 'passive-eye-movement condition' they applied a brief and gentle push to the closed tested eye before each trial.

## Results

Surprisingly, the patient had no problem with navigating an LED to body-midline. She was as accurate (Figure 6 A, left side) and precise (Figure 6 B, left side) as the control group.

To check whether the processing of eye proprioceptive input was indeed disturbed in the patient, we applied passive eye movement before each trial and measured its consequence on visual localization in the same task. This was achieved by asking the participants to briefly close and push their viewing eye before each trial. If the processing of eye proprioception was disturbed, a push should lead to an erroneous perception of eye position and therefore to mislocalization of the LED relative to the body. In accord with this prediction, RW after the passive eye movement RW showed a significant error of  $\sim 16^\circ$  in the direction of push and a larger standard deviation than controls (Figure 6). This shift was specific to the contralesional left eye. For the ipsilesional right eye, no significant changes were found.



**Figure 6. Accuracy and precision for locating an LED relative to the body in monocular vision in darkness.** Mean error (A) and standard deviation (B) for the patient (●) and a group of nineteen healthy controls (○) are shown in baseline and in push condition for the left eye. Values with one standard deviation. The arrow on the x-axis label shows the direction of the push. \* denotes a p-value  $< 0.05$  for a single-case t-test testing for a difference between the patient and the control group,  $n=19$

## Discussion

We found a significant shift of perceived eye position in patient RW that occurred only in the condition with passive eye movement. The illusion of persistent eye rotation after a brief push to the eye suggests an abnormal proprioceptive signal

after a lesion of the somatosensory cortex. This abnormal signal is incorporated into the eye position estimate only in a condition with acute mismatch, i.e. after a brief push to the eye. When the CD and proprioception are in their usual, long-term correspondence (i.e. after a chronic lesion), proprioception does not contribute to the eye position estimate.

This results explains the contradiction in previous experimental results. Studies, based on this correspondence show no change when proprioception is cut out on the long-term (Guthrie et al., 1983; Lewis et al., 1998), similar to our no-push condition. However, in studies where eye proprioception is manipulated to show an acute mismatch, there is an effect on visual localization (Gauthier et al., 1990), like in our push-condition. Based on this result, a current model for a multimodal integration state could be an average, weighted by reliability of the signal.

However, here I propose another model, that differs from the current idea that all available signals are used and weighted relative to one, fixed criterion such as reliability. It suggests that the criterion may differ with task demands, i.e. sometimes the criterion may be speed, other times accuracy or reliability.

Given that action and perception have different time constraints, we wondered whether the eye position signal for perception is optimized for accuracy/reliability, and hence uses eye proprioception (Experiment 2.1), whereas the eye position signal for action is optimized for speed, and hence relies on CD alone (Experiment 2.2).

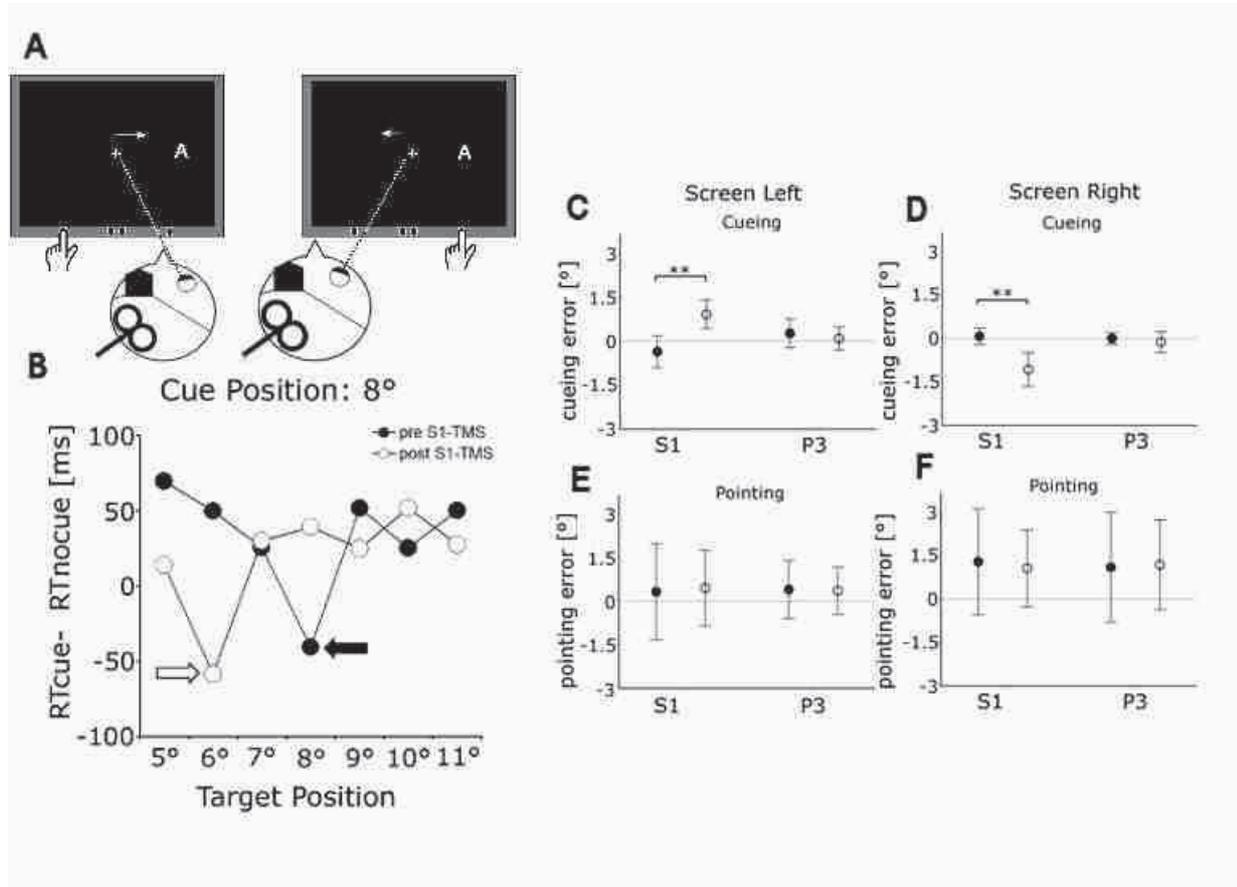
## **Experiment 2.1 - Does eye proprioception affect the eye position estimate in a cross-modal attention task (visual localization for perception)?**

(**Paper 4.** Bartholomäus Odoj & Daniela Balslev (2016). *Role of oculoproprioception in coding the locus of attention.* **J Cogn Neurosci**, 28(3), 517-528.)

### ***Methods***

To assess locus of attention, I first presented a cue in a non-visual modality (the location of subject's unseen finger), followed by the visual target that could appear at various locations around the cue (Figure 7, A). The variation in the reaction time for letter identification with distance from cue gives a measure of how attention

is allocated. The locus of attention in response to the cue is the target location with the largest decrease in reaction time in the presence compared with absence of the cue. Cueing error is the distance between the cue and the locus of attention (Figure 7, B). If an oculomotor signal is important for attending but not for reaching, then perturbing the signal should cause cueing rather than reaching errors.



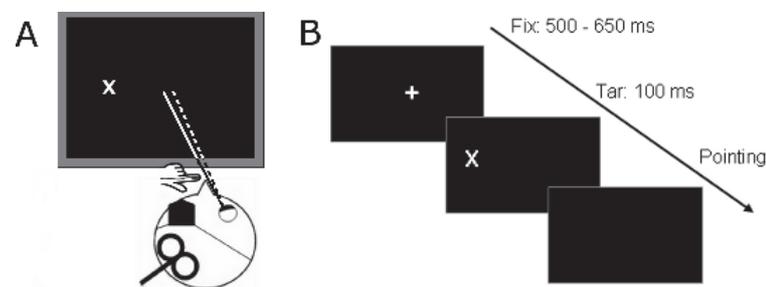
**Figure 7. S1-rTMS causes cueing rather than reaching errors.** **A.** Setup for the attention task in total darkness. The arrow indicates perceived direction of gaze after S1-rTMS, towards the midline. **B.** Example showing a left-shift in the locus of attention after S1-rTMS in one participant while tested with the right display. The cue was the position of the left index finger, ipsilateral to the TMS site, placed at 8° right of body midline. The locus of attention, indexed by the largest benefit in RT in the presence vs. in the absence of the cue, is indicated by the arrows (solid arrow before rTMS, empty arrow, after rTMS). **C-D.** Increased cueing error towards midline after S1-rTMS, in the same direction as the shift in perceived eye position. We found no effect of control rTMS over the posterior parietal cortex (P3). **E-F.** No effect of S1-rTMS on object localization as assessed by open loop pointing with the left finger to the letter (● pre-rTMS, ○ post-rTMS, mean ± SD; \*\* p<0.01, paired samples t-test, N=10 subjects).

## Experiment 2.2 - Does eye proprioception affect visual localization in a visual open-loop pointing task (visual localization for action)?

(Paper 4. Bartholomäus Odoj & Daniela Balslev (2016). *Role of oculoproprioception in coding the locus of attention*. *J Cogn Neurosci*, 28(3), 517-528.)

### Methods

Participants pointed to visual targets located at the same horizontal distance from fixation as in Experiment 2.1 (Figure 8). We predicted that visual localization for action does not depend on eye proprioceptive information. Therefore neither cTBS over S1<sub>EYE</sub>, nor over P3 was expected to have an effect on visual open-loop pointing.



**Figure 8. Setup and task for Experiment 2.2** In right eye vision, participants fixated at  $\pm 15^\circ$  from orbit center, while a position marker was attached to their left index finger, which was positioned at a starting position at body-midline (A, here: fixation at  $-15^\circ$ ). In visual pointing, a target (letter 'X') was presented for 100 ms at 1 of 4 possible target positions:  $\pm 8^\circ$ ,  $\pm 18^\circ$ ,  $\pm 20^\circ$ ,  $\pm 30^\circ$  (B). Participants closed their eyes and pointed at target position. The pointing error from target position was recorded and compared between different sessions (pre- and post-cTBS over S1<sub>EYE</sub> and P3). Solid line: eye position at fixation. Dotted line: perceived eye position after S1<sub>EYE</sub>-cTBS.

## Results for Experiments 2.1 and 2.2

After S1<sub>EYE</sub>-cTBS, the mean cueing error shifted  $\sim 1^\circ$  towards the middle of the head/body. This was towards the right for the left screen (Figure 7, C) and to the left for the right screen (Figure 7, D) for all participants. After P3-cTBS no significant shift in cueing behavior could be observed.

As expected, no shift in mean pointing error after S1<sub>EYE</sub>- or P3-cTBS could be found neither for left (Figure 7, E) nor for right screen placement (Figure 7, F).

## **Discussion for Experiments 2.1 and 2.2**

The results of Experiment 2.1 suggest that eye proprioception is used as the eye position signal for the priority map that supports cross-modal attention. This conclusion dovetails nicely with the similarities between the latency for updating of priority maps (Golomb, Chun, & Mazer, 2008) and the time it takes the eye proprioceptive signals to reach the cortex (Y. Xu, Wang, Peck, & Goldberg, 2011).

The lack of a change in pointing behavior after cTBS (Experiment 2.2) suggests that eye proprioception is not used as eye position signal in visual localization for action and is in line with a number of previous findings (Joiner et al., 2013; Lewis et al., 1998; Steinbach, 1986). This finding supports the hypothesis that the eye position signals in the gaze estimate vary depending on the behavioral goal, i.e. action or perception. Here, the CD seems to be the main source for eye position information. However, one could argue that the change in cueing error (Experiment 2.1) was not due to a shift in allocating attention, but resulted from a misperception of the position of the index finger, which led to a mislocalization of the cue position, independent from eye proprioception. To rule out this possibility, we conducted a control experiment.

### **Experiment 3. - Does S1<sub>EYE</sub>-cTBS disturb the felt position of the left index finger without affecting visual pointing accuracy?**

(**Paper 4.** Bartholomäus Odoj & Daniela Balslev (2016). *Role of oculoproprioception in coding the locus of attention.* **J Cogn Neurosci**, 28(3), 517-528.)

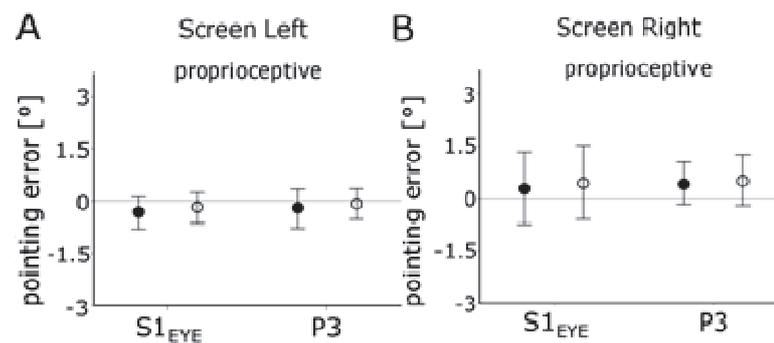
#### ***Methods***

The participants were tested, using the same cTBS-design and same setup as in experiment 2.2 (Figure 8). At the start of each trial, the experimenter led the participants left index finger towards one of the same targets as in experiment 2.2 and then

back to a starting position. Participants kept their eyes closed during the whole experiment and pointed to this proprioceptively felt target before and after cTBS over S1<sub>EYE</sub>/P3. We predicted no changes in pointing after cTBS.

## Results

No shift in mean pointing error after S1<sub>EYE</sub>-cTBS or P3-cTBS could be found neither for left screen placement (Figure 9, A) nor for right screen placement (Figure 9, B).



**Figure 9. No change in pointing after S1<sub>EYE</sub>-cTBS.** The mean pointing error in in proprioceptive pointing for left (A) and right (B) screen position is shown before (●) and after (○) cTBS over S1<sub>EYE</sub> and P3. n=10 participants, values with one standard deviation.

## Discussion

Since the perceived left finger position is not disturbed by S1<sub>EYE</sub>-cTBS, we can rule out that the systematic errors in cueing in experiment 2.1 despite accurate pointing in experiment 2.2 underlie disturbed finger proprioception.

## General Discussion: Eye position and Visual Localization

Experiments 1 to 3 show that the eye position signals (eye proprioception and CD) are not always integrated in the eye position estimate. The slow, eye proprioceptive signal contributes to visual localization only in certain circumstances – when the two eye position signals show an acute mismatch (Experiment 1) or when the goal of the task is visual discrimination rather than visually guided reaching.

This result is difficult to explain in the framework of the current model for multimodal integration. Since there were no changes in visual input or ways of stimulation, the different composition of the eye position signal cannot be explained by one fixed criterion like reliability.

A possible explanation could be that the multimodal signals are optimized flexibly. This criterion could be speed, accuracy or reliability, depending on the task demands. This hypothesis should be investigated in further experiments.

## 2. Eye Position and Visuospatial Attention

Balslev and colleagues (Balslev, Gowen, et al., 2011) hypothesized that the eye position signal from S1<sub>EYE</sub> is incorporated into the priority map. If this is the case, then the shift in the locus of attention after S1<sub>EYE</sub>-TMS must be spatially congruent with the shift in perceived eye position triggered by S1<sub>EYE</sub>-TMS. Here we investigated this prediction. Experiments 5, 6.1 and 6.2 investigate this hypothesis and also check whether a chronic lesion in S1<sub>EYE</sub> shows congruent results as a acute mismatch after S1<sub>EYE</sub>-TMS.

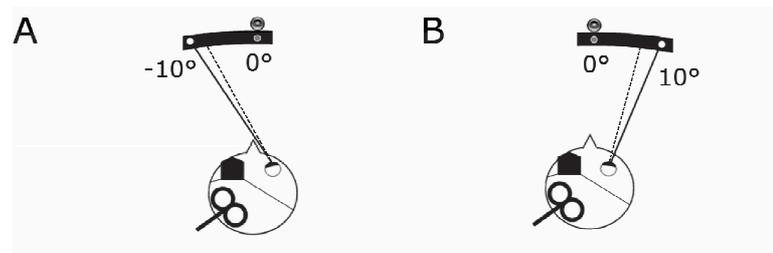
### Experiment 4. - Does cTBS over S1<sub>EYE</sub> shift perceived eye position?

(**Paper 2** - Bartholomäus Odoj & Daniela Balslev (2013). *Visual sensitivity shifts with perceived eye position*. **J Cogn Neurosci**, 25(7), 1180-1189.)

#### *Methods*

Oculomotor structures code the direction of saccades to both, auditory and visual targets, in an eye-centered reference frame (Jay & Sparks, 1984; Russo & Bruce, 1994). Saccades to visual targets can be planned in an eye-centered frame of reference, without information about eye position at saccade onset. In contrast, auditory targets are initially coded relative to ears and head. Therefore, knowledge of eye position is critical for planning saccades to sounds. We measured saccade amplitudes from lateral, visual fixation points to a central auditory or visual target before and after S1<sub>EYE</sub>- and M1-cTBS. We hypothesized that cTBS over S1<sub>EYE</sub> decreases eye

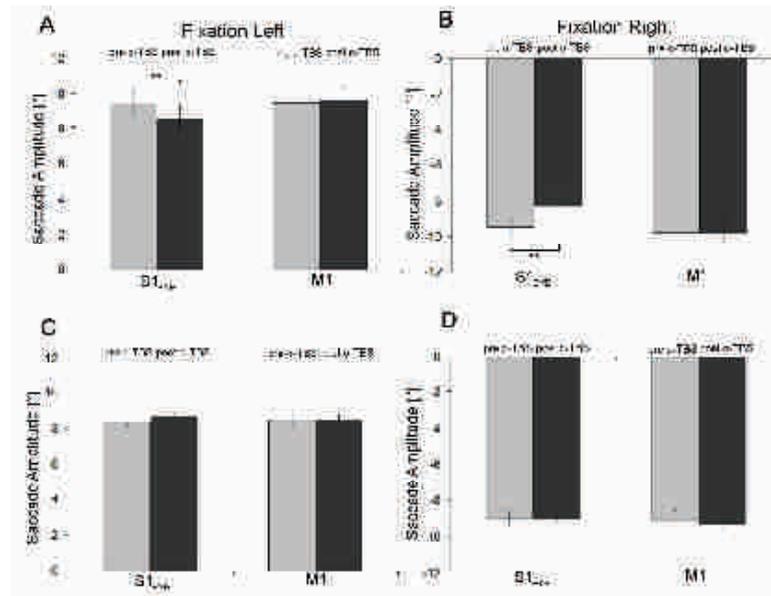
proprioception and leads to an underestimation of eye rotation during lateral fixation (Figure 10, dotted line). We predicted that saccades to auditory targets, depending on eye position information, are shorter after S1<sub>EYE</sub>-cTBS (but not after M1-cTBS). Saccades to visual targets, not depending on eye position, should not be affected by cTBS.



**Figure 10. Setup for Experiment 4.** Participants sat head-fixed in darkness with their left eye patched, fixating an LED at either  $-10^\circ$  (A) or  $+10^\circ$  (B) from body midline, so that the right eye was rotated leftward or rightward (continuous line). A saccade target, an LED or a sound burst, was presented at  $0^\circ$  (straight ahead) and extinguished before the onset of the eye movement. We hypothesized, that cTBS over S1<sub>EYE</sub> results in an underestimation of eye rotation for both directions (perceived eye position after cTBS: dotted line).

### **Results**

As expected, after S1<sub>EYE</sub>-cTBS, saccades from a lateral fixation to a central auditory target were  $\sim 1^\circ$  shorter compared with the pre-cTBS and the M1-cTBS control, causing errors to the left for leftward fixation and to the right for rightward fixation (Figure 11).



**Figure 11. Shift in perceived eye position toward orbit midline after S1<sub>EYE</sub>-cTBS.** S1<sub>EYE</sub>-cTBS shortened the saccades to auditory targets (A–B), while leaving the saccades to visual targets unchanged (C–D). This reduction in saccade amplitude was specific to the stimulation site S1<sub>EYE</sub> and did not occur after M1-cTBS. n = 14 participants, values with standard error of mean. \*\*p < .01, using Tukey's test.

### Discussion

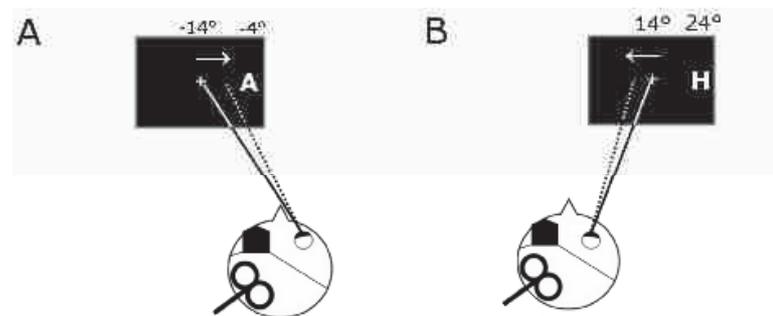
The results suggest that S1<sub>EYE</sub>-cTBS causes an underestimation of the perceived eye position: saccades to auditory targets, which depend on eye position at the onset of the saccade, are shorter only after S1<sub>EYE</sub>-cTBS. As expected, saccades to visual targets were not affected by cTBS. The shift of perceived eye position towards orbit midline from both lateral fixations is in accord with the neuronal organization present in monkeys (Wang et al., 2007) and also assumed in humans (Balslev & Miall, 2008). To establish functional congruency between eye proprioception and visuospatial attention, we tried to show a spatial congruency between the shift of perceived eye position and a shift in visual sensitivity. We predicted disturbed S1<sub>EYE</sub>-information, due to acute S1<sub>EYE</sub>-cTBS or a chronic S1<sub>EYE</sub>-lesion, shifts visual sensitivity towards the center of the orbit, the same direction perceived eye position is shifted here.

## Experiment 5.1 - Does S1<sub>EYE</sub>-cTBS shift visual sensitivity?

(Paper 2 - Bartholomäus Odoj & Daniela Balslev (2013). *Visual sensitivity shifts with perceived eye position*. *J Cogn Neurosci*, 25(7), 1180-1189.)

### Methods

Participants fixated the middle of a screen centered 14° left/right from orbit-midline and discriminated a letter presented equidistant left/right from fixation (Figure 12) before and after S1<sub>EYE</sub>- and M1-cTBS. Under the assumption that the eye proprioceptive signal from S1 eye is integrated into the priority map, we expected that visual sensitivity shifts after S1<sub>EYE</sub>-cTBS congruently with perceived eye rotation. Therefore we predicted faster reaction times for targets on the right side during left side fixation and vice versa.



**Figure 12. Setup for Experiment 5.1 and 5.2.** In right eye vision participants fixated at  $\pm 14^\circ$  to the left (A) or right (B) from the center of the orbit. A target letter, “A” or “H” was presented for 120 ms in the left or right hemifield at  $10^\circ$ . The continuous line (A–B) shows the actual direction of gaze at fixation and the dashed line shows the perceived direction of gaze according to the results of Experiment 2. The arrows show the direction of the expected increase in visual sensitivity, in the same direction as the shift in perceived eye position during Experiment 2.

## Experiment 5.2 - Does a chronic lesion in S1<sub>EYE</sub> affect visual sensitivity?

(Paper 3 - Daniela Balslev, Bartholomäus Odoj, & Hans-Otto Karnath (2013). *Role of somatosensory cortex in visuospatial attention*. *J Neurosci*, 33(46), 18311-18318.)

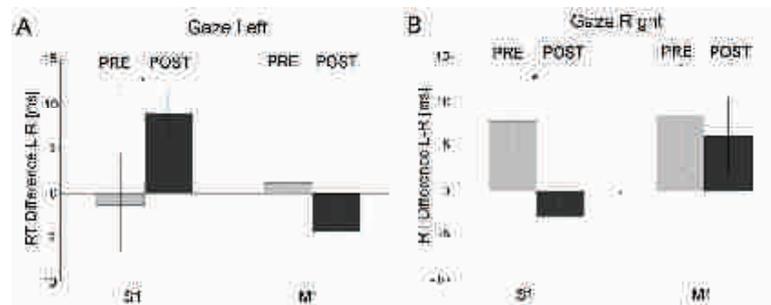
### Methods

We repeated the letter discrimination task (Experiment 5.1, Figure 12) in RW and a group of controls. According to our hypothesis, we predicted a lateral reaction

time bias in RW for targets closer to the center of the orbit, namely for targets on the right, when the eye is rotated to the left and vice versa, compared to the control group.

## Results for Experiments 5.1 and 5.2

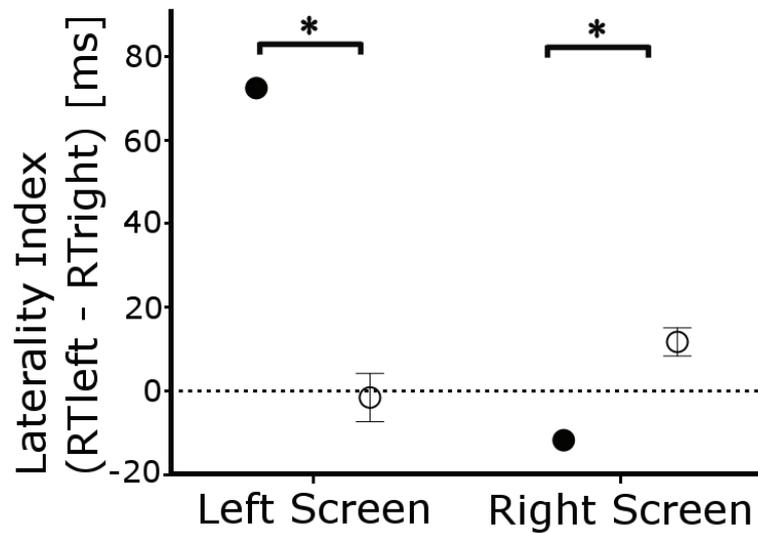
As expected, we found that S1<sub>EYE</sub>-cTBS (but not M1-cTBS) changed the left–right gradient in the RT for letter discrimination to favor locations nearer the center of the orbit: in leftward gaze, the difference in RT for left minus right targets increased ~15 ms (Figure 13, A) and in rightward gaze, the difference decreased ~10 ms (Figure 13, B).



**Figure 13. Increase in visual sensitivity toward orbit midline after S1<sub>EYE</sub>-cTBS.**

After S1<sub>EYE</sub>-cTBS, the gradient in RT between the left minus right hemifield increased in leftward gaze showing a perceptual advantage for right hemifield targets (A) and decreased in rightward gaze, showing an advantage for left hemifield targets (D). L, left; R, right, n = 13 participants, values with standard error of mean. \*p < .05, using Tukey's test

Likewise, an S1 lesion influenced the allocation of attention in the visual space to benefit locations near the midline (Figure 14). For left screen position, the calculated laterality index (reaction time for targets presented left from fixation minus reaction time for targets presented right from fixation) was significantly higher in RW compared to the controls (+ 74 ms). For right screen position, the laterality index was significantly lower in RW compared to controls (- 24 ms).



**Figure 14. Increased visual sensitivity at locations nearer the midline after a right S1<sub>EYE</sub> lesion.** For left screen position RW (●) had a significantly higher laterality index (Reaction time for targets presented left from fixation minus reaction time for targets presented right from fixation) in a left eye letter discrimination task, than the healthy control group (○, n=11). For right screen position, RW's laterality index was significantly lower. \* $p < 0.05$  for a single case t-test for a difference between patient RW and the control group (Crawford & Howell, 1998).

## Discussion for Experiments 5.1 and 5.2

We were able to reproduce the results from Balslev *et al.* (2011). In addition, the results confirmed our prediction that S1<sub>EYE</sub>-cTBS shifts visual sensitivity towards the center of the orbit, the same direction as for perceived eye position (Experiment 2.1). This finding is in line with the suggestion that the oculoproprioceptive signal is integrated into the priority map.

The experiments in the patient with a chronic S1 lesion (Experiment 1, Experiment 5.2) suggest that this signal is specific for visuospatial attention. Although after chronic lesion in S1<sub>EYE</sub> perceived eye position was not altered (Experiment 1, no-push condition), the patient showed a spatial asymmetry in the ability to discriminate retinally identical targets. An impaired eye proprioceptive information in S1<sub>EYE</sub> after a lesion shifts visual sensitivity towards the center of the orbit, in the same direction as a TMS induced “virtual lesion” (Experiment 5.1).

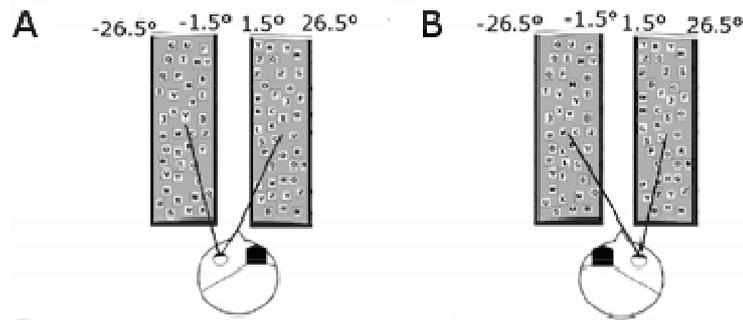
Another measurement for the allocation of attention are exploratory eye movements in a visual search task (Karnath et al., 1998). In contrast to the previous, covert attention experiments, for visual search tasks overt attention is used. Since Koch and colleagues propose their model of salience maps for both, covert and overt attention (Itti & Koch, 2000), the model of priority maps as well could control overt attention. In favor of this idea speaks the premotor theory of attention of Rizzolatti and colleagues (Rizzolatti et al., 1987), which implies that eye movements are also planned in covert attention tasks. Patients with an attention deficit like spatial neglect show an ipsilesional shift in the distribution of exploratory eye movements (H. O. Karnath, 1994). We wondered whether overt attention too is influenced by an S1 lesion.

### **Experiment 6. Does a lesion in S1<sub>EYE</sub> influence exploratory eye movements during visual search?**

(**Paper 3** - Daniela Balslev, Bartholomäus Odoj, & Hans-Otto Karnath (2013). *Role of somatosensory cortex in visuospatial attention*. **J Neurosci**, 33(46), 18311-18318.)

#### ***Methods***

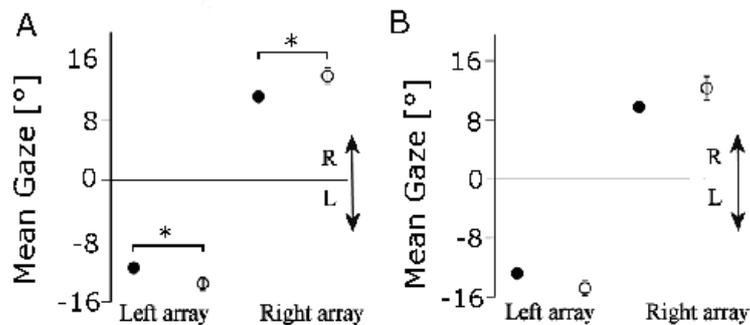
We tested patient RW in the visual search task against a group of controls. Participants searched for a non-existing target letter in a letter array centered at left or right from orbit midline (Figure 15). We assumed that a chronic lesion in S1<sub>EYE</sub> causes a bias in exploratory eye movements during visual search that depends on the direction of eye rotation, similar to the bias in visual sensitivity (Experiments 5.1 and 5.2).



**Figure 15. Setup for Experiment 7.** Participants searched for a nonexistent letter A in a 25°-wide array centered at 14° to the left and right of the orbit center of the left (A) and right (B) eye. Mean gaze position was measured (solid line) and compared between RW and the control group

### Results

We found that RW's mean gaze was significantly shifted  $\sim 2^\circ$  towards the midline, that is to the right during visual search in the leftward letter array and to the left for the rightward array (Figure 16). This shift was caused by a shift in spatial distribution of the fixation time. Range of eye movements and number of fixations in the left/right letter arrays did not differ between RW and the control group.



**Figure 16. A focal, right S1<sub>EYE</sub> lesion shifts mean gaze during visual search towards orbit midline.** In left (contralateral) eye visual search (A), RW's mean gaze position (●) is significantly closer to the orbit midline, namely more to the right in left array search and more to the left in right array search, compared to a age-matched healthy control group (○, n=11). In right (ipsilateral) eye visual search (B), similar results are not significant. Zero corresponds to the position of the midline of the orbit on a horizontal line. \* $p < 0.05$  for a single case t-test for a difference between patient RW and the control group (Crawford & Howell, 1998).

## ***Discussion***

The bias of looking time towards the inner region of the array is congruent with the shift of visual sensitivity found in this patient and the TMS study (Experiments 5.1 and 5.2). RW's bias in looking time towards the center of the orbit despite normal oculomotor ability again suggests that S1<sub>EYE</sub> plays a role in the allocation of attention in the body-centered space.

Patients with hemispatial neglect after a right perisylvian stroke manifest a noticeable eye deviation to the right (ipsilesional) hemifield (H.-O. Karnath, 1994). They also show a shift in spatial attention as well as in exploratory eye movements during visual search to the right. RW shows an attentional shift to the left for visual sensitivity as well as for exploratory eye movements, when eyes are rotated to the right. This raised the question, whether a coinjury in S1<sub>EYE</sub> is associated with milder neglect.

### **Experiment 7. Does a coinjury in S1<sub>EYE</sub> together with perisylvian lesions have an effect on hemispatial neglect?**

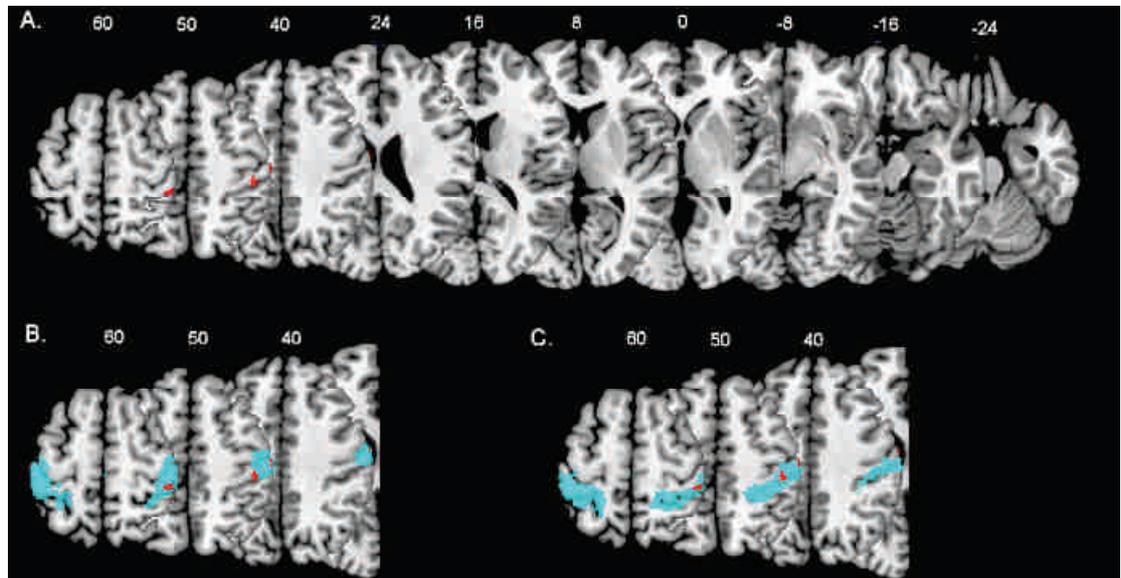
(**Paper 3** - Daniela Balslev, Bartholomäus Odoj, & Hans-Otto Karnath (2013). *Role of somatosensory cortex in visuospatial attention*. **J Neurosci**, 33(46), 18311-18318.)

## ***Methods***

To analyze, whether a coinjury in S1<sub>EYE</sub> together with lesions in the perisylvian network, an area most likely to cause hemispatial neglect (Karnath & Rorden, 2012), has an effect on the severity of hemispatial neglect, we performed a voxelwise lesion behavior mapping (VLBM) including stroke patients with perisylvian lesions. As a measure of neglect severity, we used the Center of Cancellation, or CoC (Rorden & Karnath, 2010). The patient imaging and behavioral data were entered into the VLBM analysis, using the CoC as dependent variable, identifying voxels whose lesion correlate with neglect severity. We predicted that an additional lesion in S1<sub>EYE</sub> correlates with a lower neglect score.

## Results

We found that a lesion in S1<sub>EYE</sub> indeed correlated with a lower neglect score (Figure 17). The groups (coinjury of S1<sub>EYE</sub> vs. no coinjury of S1<sub>EYE</sub>) did not differ significantly in lesion size, age or testing time after lesion.



**Figure 17. Brain areas in which an additional lesion was associated with milder neglect, given a primary lesion in the perisylvian network region.** The statistical map (red) is thresholded at  $p < 0.05$ , FDR corrected ( $z$  score  $> 2.16$ ) and overlaid on a single-subject T1 template coregistered with the MNI152 template (A). The probabilistic maps from the Juelich atlas for BA 1 (B) and BA 2 (C) thresholded at a voxel probability for the BA = 25% are shown in blue.

## Discussion

When an S1<sub>EYE</sub> lesion occurs as a part of a large perisylvian stroke it is associated with a reduced attentional bias towards the ipsilesional space and thus with a milder neglect. The results support the hypothesis, that S1<sub>EYE</sub> is a node in the visuospatial attention network.

## General Discussion: Eye Position and Visuospatial Attention

The result from experiments 5.1, 5.2, 6 and 7, as well as from experiment 2.1, show that the somatosensory cortex, presumably the eye proprioceptive area  $S1_{EYE}$  has an influence on the allocation of attention in the visual space. Neither  $S1$  nor the oculoproprioceptive signal have previously been associated with visuospatial attention. However, these results are in line with the well-known neuroanatomical and functional coupling between the oculomotor and visuospatial attention systems. There are two possibilities for a functional coupling between oculoproprioception and spatial attention.

First, the function in  $S1_{EYE}$  in spatial attention and in eye position coding could rely on independent neural populations, that share the same principle of organization. An example for such an organization can be found in the FEF, where separate neural populations code saccade directions and attentional shifts (Juan, Shorter-Jacobi, & Schall, 2004).

Second, it is also possible, that the locus of attention is coded with the use of an eye position signal with a proprioceptive component. This explanation is compatible with the delay in updating the locus of attention after an eye movement of 100-200 ms (Golomb et al., 2008) and the latencies of  $\sim 150$  ms in which gain field neurons modulate neuronal activity in the LIP after an eye movement (Andersen & Mountcastle, 1983).

Regardless of the exact neuronal mechanisms, we can conclude that the eye proprioceptive signal in  $S1_{EYE}$ , although it plays a minor role in locating visual objects relative to the body (Experiments 1, 2.2 and 3), affects the allocation of attention in visual space.  $S1_{EYE}$  should be seen as a part of the visuospatial attention network.

## ***VIII. Conclusions***

### **1. ) CD is normally used as main eye position signal in visual localization.**

Although eye proprioception is continuously monitored, visual localization normally relies on CD. However, in case of a mismatch between the two sources of information, eye proprioception is taken into account, presumably to restore accuracy.

### **2. ) The eye position estimate is flexible and depends on the task demands.**

Here we propose a model for a multimodal integration state, that doesn't use one fixed criterion like reliability, but a flexible one, which varies with the task demands. The eye position estimate for action seems to be optimized for speed and uses the CD, while the eye position estimate for perception could be optimized for accuracy and uses eye proprioception.

### **3.) S1 is a part of the visuospatial attention network.**

Our experiments have shown that the somatosensory cortex has a direct influence on the allocation of attention. This novel role of this brain area can be explained by either a) two independent, similar organized neural populations in S1<sub>EYE</sub>, one that controls attention and the other that senses eye position or b) a direct use of a proprioceptive gaze-direction signal in the priority map to support body- or object-centered representations.

## ***IX. Limitations of the current experiments and further questions***

### ***TMS related constraints in data interpretation***

There are three aspects of TMS, that have to be taken into consideration, when interpreting the data.

First, the resolution of the method does not allow to conclude whether neural populations that are responsible for changes in visual sensitivity (Experiment 3) are the same as those that code the direction of gaze. For instance this is the case in the FEF, where different neural populations code the directions of saccades and attention shifts (Juan et al., 2004; Thompson, Biscoe, & Sato, 2005). Electrophysiological experiments in monkeys, which measure neuronal activity on directly could help tell the two hypotheses apart.

Second, the TMS-induced electric field can spread both, locally to adjacent areas, as well as remotely, through neural connections. Therefore it can not be excluded, that changes in performance do not arise from the area under the coil, but rather from regions near the somatosensory cortex. However, an effect induced by a spread to other regions seems unlikely because of two reasons. First, we did not find any effects after stimulation of our control sites. M1 is anatomically closer to the eye muscles or oculomotor structures like the FEF. Inhibitory TMS over P3 is known to bias visual exploration or stimuli perception. Therefore we should find even larger effects after cTBS over the control sites compared to a spread-induced effect after S1<sub>EYE</sub>-cTBS. Second, results from previous studies, in which TMS was directly applied over P3/P4 or the FEF (Hilgetag et al., 2001; Nyffeler et al., 2008) differ from the gaze-dependent results we found after S1<sub>EYE</sub>-cTBS.

At last, for our experimental setup, we did not take TMSA into account. For future experiments it could be helpful to perform intensive training sessions, maybe with different targets, affecting different neural populations, before the experiment. This should optimize the TMS-effect and also give a more selective way to analyze it's impact on different neural population groups.

### ***In what frame of reference is the attention shift coded?***

The setup of our attention experiments does not allow to tell, whether the found shifts of attention occurred relative to a reference frame centered on the orbit, head, or trunk. An orbit centered reference frame would strengthen the association between attention and oculoproprioception. Further experiments that dissociate head and trunk midline by asking the subjects to rotate their head on the trunk could address this question.

### ***How is $S1_{EYE}$ connected with the spatial attention network?***

Studies applying fMRI in patients with a lesion in  $S1_{EYE}$  could help to investigate, where and how precisely  $S1_{EYE}$  is involved in the visual processing stream and in triggering motor responses. fMRI studies in healthy participants could help to identify brain regions coding priority maps in body-centered coordinates and their eye position input.

## ***X. Abbreviation list***

CD	-	corollary discharge
CNS	-	central nerve system
CoC	-	center of cancellation
cTBS	-	continuous theta-burst stimulation
EEG	-	electroencephalography
EOM	-	extra-ocular muscles
FDA	-	U.S. Food and Drug Administration
FDI	-	first dorsal interosseous (FDI) muscle
FEF	-	frontal eye field
fMRI	-	functional magnet resonance tomography
GTOs	-	Golgi tendon organs
LED	-	light-emitting diode
LIP	-	lateral intraparietal cortex
LTD	-	long-term depression
LTP	-	long-term potentiation
M1	-	primary motor cortex
MD	-	mediodorsal thalamus
MEG	-	magnetoencephalography
MEP	-	motor evoked potential
MT	-	visual area middle temporal
(r)TMS	-	(repetitive) transcranial magnetic stimulation
TMSA	-	TMS adaptation
S1 <sub>EYE</sub>	-	eye proprioceptive area in the primary somatosensory cortex
SC	-	superior colliculus
VLBM	-	voxelwise lesion behavior mapping

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# Eye Proprioception Used for Visual Localization Only If in Conflict with the Oculomotor Plan

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Both the corollary discharge of the oculomotor command and eye muscle proprioception provide eye position information to the brain. Two contradictory models have been suggested about how these two sources contribute to visual localization: (1) only the efference copy is used whereas proprioception is a slow recalibrator of the forward model, and (2) both signals are used together as a weighted average. We had the opportunity to test these hypotheses in a patient (R.W.) with a circumscribed lesion of the right postcentral gyrus that overlapped the human eye proprioceptive representation. R.W. was as accurate and precise as the control group ( $n = 19$ ) in locating a lit LED that she viewed through the eye contralateral to the lesion. However, when the task was preceded by a brief ( $< 1$  s), gentle push to the closed eye, which perturbed eye position and stimulated eye proprioceptors in the absence of a motor command, R.W.'s accuracy significantly decreased compared with both her own baseline and the healthy control group. The data suggest that in normal conditions, eye proprioception is not used for visual localization. Eye proprioception is, however, continuously monitored to be incorporated into the eye position estimate when a mismatch with the efference copy of the motor command is detected. Our result thus supports the first model and, furthermore, identifies the limits for its operation.

## Introduction

Without knowledge of eye position it would be difficult to match a person and a voice in a crowd, to plan an eye movement toward a salient noise or to reconstruct the spatial relationships in a visual scene from retinal snapshots. Despite a century-long debate about efference copy versus sensory reafference the question whether visual localization relies on the corollary discharge (von Helmholtz, 1925) or eye proprioception (Sherrington, 1918) is still unanswered and experimental observations seem contradictory. On one hand, the CNS receives proprioceptive eye position information—e.g., humans are aware of the passive displacement of the eyes in darkness (Skavenski, 1972)—and altering this proprioceptive information consistently leads to errors in visual localization (Campos et al., 1986, 1989; Gauthier et al., 1990; Bridgeman and Stark, 1991; Allin et al., 1996; Lennerstrand et al., 1997; Balslev and Miall, 2008). This line of evidence suggests that the afferent, proprioceptive input contributes to the estimate of eye position. On the other hand, in the monkey, bilateral section of the trigeminal nerves, which carry ocular proprioceptive information to the brain (Porter et al., 1983), does not reduce the

accuracy or the precision of open-loop pointing (Lewis et al., 1998), suggesting that the efference copy is sufficient and eye proprioception not necessary for visual localization.

Prompted by the recent discovery of an eye proprioceptive signal in area 3a in the monkey (Wang et al., 2007; Xu et al., 2011) and in the postcentral gyrus in humans (Balslev and Miall, 2008; Balslev et al., 2011) we have re-examined the question of whether eye proprioception contributes to locating stimuli in relation to the body in a patient (R.W.) with a focal lesion of the postcentral gyrus. Her lesion overlapped the proprioceptive representation of the extraocular muscles from both eyes as previously identified with fMRI in healthy humans (Fig. 1) (Balslev et al., 2011). A deficit in eye proprioception was therefore presumed.

Visual localization was tested in darkness and monocularly using a task where the subjects had to place an LED straight in front of the nose (Gauthier et al., 1990; Balslev and Miall, 2008) under two conditions, “baseline” and “push.” In one of these conditions (push) before each trial, a perturbation was applied briefly to the eye. A brief and gentle push applied on a nonviewing eye perturbs temporarily eye position without triggering a motor command (Ilg et al., 1989). In the absence of an efference copy, accurate eye position knowledge requires eye proprioception. Previous observations have shown that healthy subjects have no problem correcting for this perturbation. Their error in this condition was similar with that during the condition where no push was applied (baseline) (Balslev and Miall, 2008). If eye proprioception is incorporated into the eye position estimate we predicted that the patient will be less accurate and precise than the age-matched, healthy control group ( $N = 19$ ) in either condition. On the other hand, if proprioception is important only in condi-

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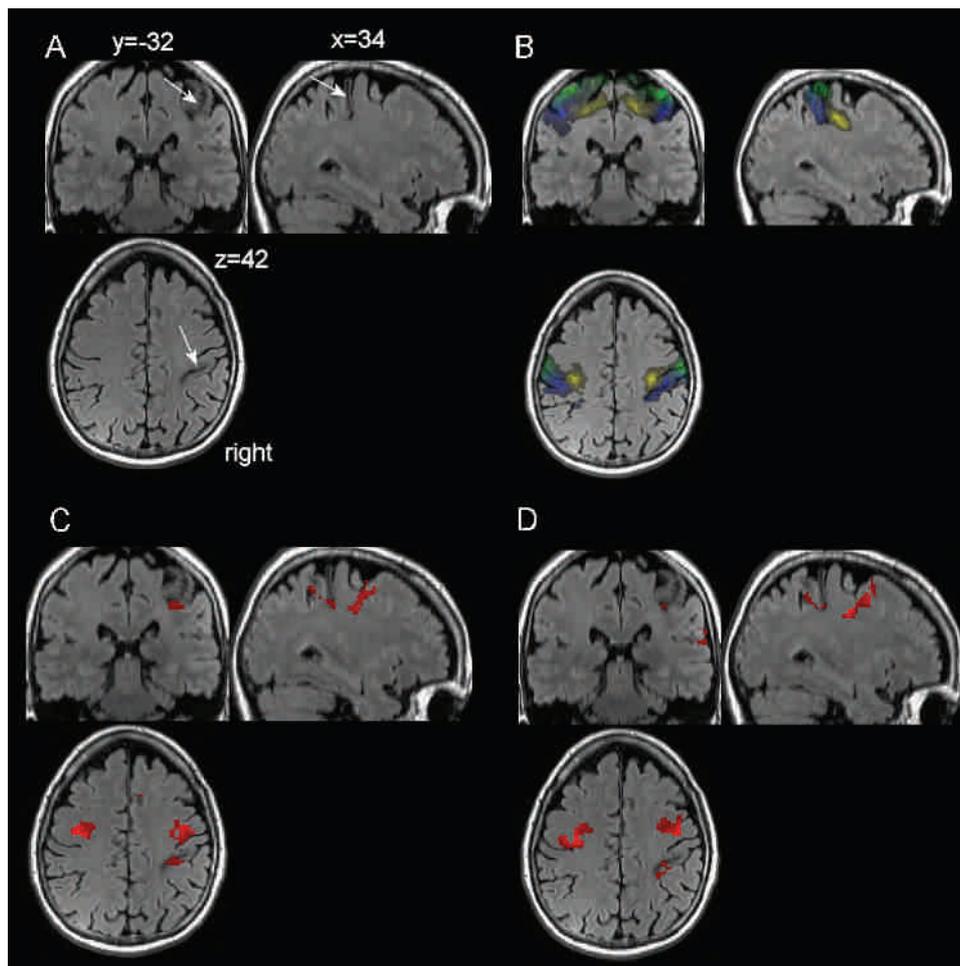
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**Figure 1.** The lesion of patient R.W. overlaps with the Brodmann Areas 3a, 1 and 2 and the cortical projection for eye proprioception in the postcentral gyrus. The lesion (arrow) is shown in 3 orthogonal projections through the coordinates ( $x, y, z = 34, -32, 42$ ) on a T1-weighted MR-image of the patient's brain normalized to the MNI space (**A–D**). In **B**, the color overlays show the probabilistic atlas for area 3a (yellow), 2 (blue), and 1 (green), probabilities 10–100%. The red overlay shows the representation of eye proprioception for the left (**C**) and the right (**D**) eye muscles as identified by fMRI in a group of 18 healthy subjects (Balslev et al., 2011). The threshold for this functional overlay is  $z$ -score  $>2.61$ ,  $p < 0.005$ , uncorrected for multiple comparisons.

tions when eye position is perturbed by an external force, then such errors should occur only in the condition with a push.

## Materials and Methods

### Subjects

**Patient R.W.** We tested the patient R.W., a 69-year-old woman, right-handed (Edinburgh handedness inventory score of 90; Oldfield, 1971) and with right eye dominance (“hole in the paper” test; Crider, 1944). Her vision was corrected to normal using glasses. R.W. had a MR-confirmed focal intracerebral hemorrhage with a length diameter of 3.6 cm centered on the right postcentral gyrus. The lesion overlapped with Brodmann Areas 3, 2, and 1 as defined by the Juelich atlas (Geyer et al., 1996; Grefkes et al., 2001; Eickhoff et al., 2005). On this atlas it was possible to localize 94.6% of the lesion volume, 80% of it being located in the primary somatosensory cortex (39.9% in Area 2, 19.7% in Area 3b, 15.9% in Area 1, and 4.5% in Area 3a). Less than 4% of the voxels were also found in Area 7 (3.9%), Area 4 posterior (3.2%), IPC (2.9%), and Area 4 anterior (2.8%). The lesion also overlapped in part with the projection of eye muscle proprioception in the sensorimotor cortex identified in healthy subjects by Balslev et al. (2011) (Fig. 1).

At the time of testing,  $\sim 3$  years poststroke, R.W. had a selective proprioceptive deficit in both hands, but normal two-point discrimination and no impairment in the ability to move or exert power (Borchers et al., 2011). Similar with the hand, we found no asymmetry in the accuracy of tactile discrimination in the eyelid region. Two-point discrimination was identical on both sides, 16 mm on the lower and 20 mm on the upper

eyelid. She reported that immediately after stroke she suffered from double vision, a symptom that resolved within a few days.

**Control group.** Nineteen healthy participants (15 women) were tested as controls (median age: 63 years, range 57–73 years). The mean age was not significantly different to the patient's age [ $t$  test, single case comparison (Crawford and Howell, 1998),  $p = 0.394$ ]. All controls were right-handed and had normal or corrected-to-normal vision. Fifteen participants had right eye dominance. Patient and controls gave written informed consent to participate in the study, which was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and approved by the local Ethics Committee.

### Visual localization task

**Baseline condition.** To investigate the effect of a lesion of the right postcentral gyrus on perceived eye position we used a task in which the participants located their visual straight ahead in monocular vision and darkness (Gauthier et al., 1990; Balslev and Miall, 2008).

The participant sat at 49 cm in front of an array with 96 LEDs separated by 1 cm/1.1°, its center aligned with the head/body midline. The head was fixed with a chin rest and cheek pads.

At the initiation of each trial one of 6 possible LEDs chosen in a predetermined random order that was identical across patient and controls was lit up (position  $-16.5^\circ, -13.2^\circ, -9.9^\circ, 9.9^\circ, 13.2^\circ, 16.5^\circ$ ; negative values denote locations to the left of head midline). The participants' task was to navigate this LED directly in front of their nose by telling the experimenter to move the LED to the left or right. This position was

recorded and a new trial started. The task comprised 24 trials, 4 for each possible start position of the LED. Visual localization error and SD were calculated.

**Passive eye displacement (push) condition.** To investigate the impact of eye proprioception on visual localization, the same task was performed immediately after a displacement of the viewing eye using a gentle and brief push (<1 s) on the closed eyelid. When applied to a closed eye this push moves the eye briefly in the direction of the push, then the eye returns toward its resting position. Because no eye movement occurs in the other eye (Ilg et al., 1989), it is unlikely that this maneuver causes an oculomotor command, and thus, the only source of information about the displacement is the extraocular muscle proprioceptors. The push condition was practiced with normal binocular vision before the start of the experiment. The participants placed their right index finger at the outer corner of the eyelid and pushed the eye bulb toward the nose, increasing the force until they produced double vision. They were instructed to reproduce the same force when pushing the eye through a closed eyelid during the experiment. Immediately after pushing the eye, the participants opened their eye to perform the task like in the baseline condition. Twelve trials per eye (two for each starting LED) were performed. For both eyes, participants pushed with their right index finger. Patient and controls performed the conditions in the same order: right eye baseline, right eye push, left eye baseline, and left eye push.

### Analysis

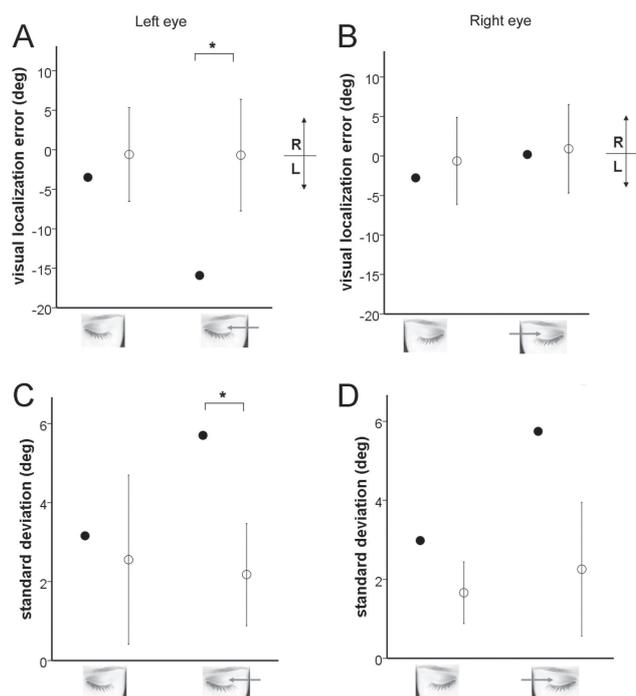
To compare R.W.'s performance in one task with the control group, we applied two-tailed *t* tests adapted for the single-case studies (Crawford and Howell, 1998). To test for a dissociation between conditions in patient R.W. an unstandardized difference test was used. This test implements a repeated-measures ANOVA for the single-case (Crawford et al., 1998; Crawford and Garthwaite, 2005).

## Results

In the baseline condition, both R.W. and the control group were accurate in locating the straight ahead position visually with either eye (Fig. 2*A,B*). The modified *t* test for the single-case comparison (Crawford and Howell, 1998) showed no significant difference between R.W. and the control group ( $p > 0.6$  for left eye;  $p > 0.7$  for right eye). Moreover, there was also no statistical evidence for an accumulation of errors in the patient from the first to the last trial of the baseline session. The regression line encoding the change in error over time had a small negative slope in the patient ( $-0.18$  for the left and  $-0.15$  for the right eye) that did not significantly differ from the control group ( $p > 0.2$  for either eye).

In the push condition, the accuracy of visual localization in the control group was similar to the baseline condition. In contrast, R.W. showed a significant error to the left by  $15.91^\circ$  for the left, contralesional, eye, which was significantly different from the control group ( $p = 0.049$ ). For the right eye, no significant difference between R.W. and the control group ( $p > 0.9$ ) was observed. A repeated-measures ANOVA implemented as an unstandardized difference test (Crawford et al., 1998; Crawford and Garthwaite, 2005) showed a highly significant difference between conditions in the patient relative to controls for the left eye (unstandardized difference test  $p < 0.001$ , correlation between baseline and push conditions in the control group  $r = 0.92$ ) and no significant interaction for the right eye ( $p > 0.7$ , correlation between conditions in the control group  $r = 0.73$ ). The left, contralesional eye was significantly more affected than the right, ipsilesional eye. In the push condition, there was a significant difference between the left and the right eye in the patient compared with controls (unstandardized difference test,  $p = 0.043$ , correlation between eyes in the control group  $r = 0.49$ ).

Results in the same direction albeit weaker were found for the SD (Fig. 2*C,D*). Again no difference was found between patient



**Figure 2.** Accuracy and precision for locating an LED relative to the body in monocular vision and in darkness. Mean error (*A, B*) and SD (*C, D*) for the patient and a group of 19 healthy controls are shown in baseline and in push condition, separately for the left eye (*A, C*) and right eye (*B, D*). Error bars represent one SD. The arrow on the *x*-axis label shows the direction of the push. Filled circles, patient; empty circles, controls; asterisk denotes a *p* value  $< 0.05$  for a single-case *t* test testing for a difference between the patient and the control group ( $N = 19$ ).

and controls in the baseline condition (single-case comparison:  $p = 0.786$  for left and  $p = 0.117$  for right eye). For the left eye, the push significantly increased the SD in the patient (Fig. 2*C*,  $p = 0.016$ ). For the right eye, a numerical difference in the same direction was found (Fig. 2*D*,  $p = 0.06$ ). The difference between conditions in the patient however did not reach statistical significance for either eye (unstandardized difference test  $p > 0.1$ , correlation  $r = 0.46$  for the left eye and  $r = 0.64$  for the right eye).

## Discussion

This study investigated whether eye proprioception contributes to visual localization. We tested whether a patient with a presumed deficit in eye proprioception after a focal lesion in the left postcentral gyrus made more errors in locating a visual target relative to the head midline compared with an aged-matched control group. Although the patient was as accurate and precise as the control group under the normal, baseline condition, she exhibited a significant error when the position of one eye was perturbed peripherally. In this condition, we found a shift to the left in perceived straight ahead when the task was executed with the left, contralesional, eye. This corresponds to a shift toward the nose in perceived eye position, in the direction of the applied force. The direction of this shift is identical with that produced by a push after 1 Hz rTMS in healthy subjects, a procedure that decreased the excitability of the eye proprioceptive area (Balslev and Miall, 2008). The illusory eye rotation induced by peripheral eye manipulation that occurs only in the context of a decreased cortical processing in the somatosensory cortex suggests that under these circumstances, an erroneous proprioceptive input is incorporated into the estimate of eye position.

The impairment in visual localization in the patient during the push condition was stronger for the left, contralesional eye. For this eye both accuracy and precision were decreased in the patient relative to the control group. For the right, ipsilesional eye, the mean error was similar with the control group whereas for the SD we found a trend ( $p = 0.06$ ) for a decrease in the precision for visual localization, similar with the left eye. Thus, despite the bilateral representation of eye proprioception in the human brain identified by fMRI (Balslev et al., 2011), the larger severity of the proprioceptive impairment in the contralesional compared with the ipsilesional eye suggests that the eye proprioceptive representation in the contralateral hemisphere has a higher functional impact.

Based on these results we argue that in normal conditions the oculomotor command is sufficient for visual localization and proprioception adds no benefit. However, the proprioceptive input seems to be used as soon as it conflicts with the estimate of eye position based on the efference copy. In this way, the healthy control group can correct for an externally imposed perturbation to eye position. In the patient with a somatosensory lesion, this information is reduced or distorted. Consequently errors in visual localization occur when the oculomotor command alone cannot indicate eye position, as in the push condition of the present experiment.

This interpretation explains previously contradictory observations. On one hand acute distortions in eye proprioceptive input after tendon vibration (Allin et al., 1996; Lennerstrand et al., 1997), passive eye movement (Gauthier et al., 1990; Bridgeman and Stark, 1991) or rTMS (Balslev and Miall, 2008) in humans alter visual localization, suggesting that proprioception contributes to this function. These observations would fit with a model where the two sources of eye position are combined as a weighted average, the weight of proprioception being calculated to be ~26–32% (Gauthier et al., 1990; Bridgeman and Stark, 1991). On the other hand, in the monkey, the reduction of the proprioceptive afference to the brain by bilateral sectioning of the trigeminal nerve does not increase either error or SD for locating a visual target during open-loop pointing (Lewis et al., 1998) suggesting that proprioception makes no contribution at all. These observations would fit with a model where proprioception, although not used for visual localization, calibrates over the long term the forward model which estimates the consequences of the oculomotor command (Steinbach, 1986). Because these two sets of experiments were performed in different species with known differences in the eye proprioceptive system (e.g., extraocular muscle spindles are absent in the monkey but present in humans; Donaldson, 2000), interspecies differences could have been responsible for the apparent contradiction between their conclusions. Another possible source of discrepancy is the concern that in the experiment by Lewis et al. (1998), despite the bilateral section of the trigeminal nerves, sufficient proprioceptive input could reach the CNS via the oculomotor nuclei, which have recently been suggested to receive sensory input from the pallasade endings (Lienbacher et al., 2011). The current experiment tested in the same subjects how visual localization is affected by both the conflict between the proprioceptive inflow and the efference copy (e.g., by comparing the baseline and the push condition) as well as by the reduction in the proprioceptive afference (e.g., by comparing the patient and the healthy group). This design allowed us to conclude that although in normal conditions proprioception is unlikely to contribute to visual localization, the afferent input is compared with the efference copy and used as soon as a discrepancy between the two sources of eye position information is de-

tected. Our observations offer thus support to both models and furthermore explain their apparent contradiction by identifying the circumstances when they operate.

The redundancy of proprioception for eye localization is at the first glance surprising. It contrasts with the findings in the skeletal system, where limb localization relies on both proprioception and the efference copy of the motor command (Wolpert et al., 1995). It is also at odds with the idea that the brain uses all available information, weighting each source according to its reliability to obtain a common, more precise estimate (van Beers et al., 2002; Ernst and Bühlhoff, 2004). Unlike the limbs that move in a relatively unpredictable environment, against gravity and at lower speed, the eyes move very fast during saccades, rest on the orbit floor cushioned in connective tissue and are unlikely to be exposed to sudden mechanical perturbations. Therefore, for the eye, neural mechanisms may have evolved to support precise feedforward control of position, rendering the slower proprioceptive feedback superfluous. However, proprioceptive information is sampled, compared with the efference copy and incorporated into the estimate of eye position as soon as discrepancies are detected. This could be the case after injury or surgery or after small mechanical perturbations of the eye bulb (e.g., applying a contact lens).

Our conclusion rests on the assumption that the comparison between the proprioception and efference copy occurs upstream S1, so that despite an S1 lesion, a mismatch between the two signals (e.g., eye push) can be correctly detected and can impact on visual localization. In humans, the ascending pathways for neither the proprioceptive input nor the efference copy of the oculomotor command are known. Single cell recordings in non-human primates have uncovered a pathway that relays the efference copy from the superior colliculus via the medial-dorsal thalamic nucleus to the cortex (Sommer and Wurtz, 2008). For eye proprioception, the subcortical pathways are less well understood, but similar with those for the efference copy, are likely to include the superior colliculus (Ndiaye et al., 2000) or the central thalamus (Tanaka, 2007), structures which are therefore plausible candidates for where the two signals converge. However, mapping the neural structures that respond to the mismatch between proprioception and efference copy (e.g., by fMRI or neurophysiological recordings) would be needed to identify how the CNS implements this comparison.

One could object that the weighted average model could explain the current data if one assumes that proprioception is weighted higher in the push compared with the no-push condition. In the push condition, this would then cause a larger difference in performance between controls and the patient, who has no proprioceptive signal, and therefore makes more systematic error and drops precision. Our arguments against this objection are the failure to find a difference in SD between patients and controls in the no-push condition as well as the similar SD in controls between the push and no-push conditions. However, since these are both null results, they should be interpreted with caution. It may be the case that the weight of proprioception in the no-push condition is so small, that the corresponding small increase in noise in the patient is swamped by other noise sources, such as output errors in aligning the stimulus to straight ahead. A similar explanation could be given for the failure to find a statistically significant increase in SD in the control group from the no push to the push condition. To test this possibility further studies using different visual localization tasks (e.g., pointing or saccades to visual targets), various target positions (e.g., not only straight ahead) or various delays between the push and the task would be needed.

In conclusion, the current data suggest that visual localization normally relies on the efference copy of the motor command, and that eye proprioception, although continuously monitored, is used only in conditions when these two sources of information mismatch.

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# Visual Sensitivity Shifts with Perceived Eye Position

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## Abstract

■ Spatial attention can be defined as the selection of a location for privileged stimulus processing. Most oculomotor structures, such as the superior colliculus or the FEFs, play an additional role in visuospatial attention. Indeed, electrical stimulation of these structures can cause changes in visual sensitivity that are location specific. We have proposed that the recently discovered ocular proprioceptive area in the human postcentral gyrus ( $S1_{EYE}$ ) may have a similar function. This suggestion was based on the observation that a reduction of excitability in this area with TMS causes not only a shift in perceived eye position but also lateralized changes in visual sensitivity. Here we investigated whether these shifts in perceived gaze position and visual

sensitivity are spatially congruent. After continuous theta burst stimulation over  $S1_{EYE}$ , participants underestimated own eye rotation, so that saccades from a lateral eye rotation undershoot a central sound (Experiment 1). They discriminated letters faster if they were presented nearer the orbit midline (Experiment 2) and spent less time looking at locations nearer the orbit midline when searching for a nonexistent target in a letter array (Experiment 3). This suggests that visual sensitivity increased nearer the orbit midline, in the same direction as the shift in perceived eye position. This spatial congruence argues for a functional coupling between the cortical eye position signal in the somatosensory cortex and visuospatial attention. ■

## INTRODUCTION

Gaze and attention are tightly coupled. This observation during everyday behavior is substantiated by the shared neuroanatomical substrates and the functional interactions between the oculomotor and visuospatial attention systems (Smith & Schenk, 2012; Rizzolatti, Riggio, Dascola, & Umiltá, 1987). Stimulation of the oculomotor structures, such as the FEFs or the superior colliculi, can not only evoke saccades (Bruce, Goldberg, Bushnell, & Stanton, 1985; Robinson, 1972) but can also create areas of increased visual sensitivity (Ruff et al., 2006; Cavanaugh & Wurtz, 2004; Moore & Fallah, 2004). These studies have established a link between the oculomotor structures and visuospatial attention. A recently discovered oculomotor structure is the eye proprioceptive area in the human somatosensory cortex ( $S1_{EYE}$ ; Balslev, Himmelbach, Karnath, Borchers, & Odoj, 2012; Balslev & Miall, 2008), presumably a homologue of the eye proprioceptive area in the monkey (Wang, Zhang, Cohen, & Goldberg, 2007). We have previously suggested that  $S1_{EYE}$ , in addition to its role in coding the rotation of the eye in the orbit, also has a function in visuospatial attention (Balslev, Siebner, Paulson, & Kassuba, 2012; Balslev, Gowen, & Miall, 2011). This suggestion was based on the following observation. Interfering with the function of  $S1_{EYE}$  by using inhibitory repetitive TMS caused lateralized changes in visual sensitivity that depended on the direction of eye rotation (Balslev et al.,

2011). For instance, when the right eye was rotated leftward, 1 Hz rTMS over  $S1_{EYE}$  decreased the accuracy for detecting left compared with right visual hemifield targets. When the right eye was rotated rightward, we found the opposite results; now the right hemifield targets were detected less accurately than those on the left. These changes in visual sensitivity were mirrored by changes in the activity of the extrastriate visual cortex after  $S1_{EYE}$ -rTMS (Balslev, Siebner, et al., 2012).

To further characterize the function of the somatosensory cortex in visuospatial attention, here we tested the hypothesis that the lateral shift in visual sensitivity induced by changing the excitability of  $S1_{EYE}$  is spatially congruent with the rTMS-induced shift in perceived gaze direction.

To this end, we tested both perceived direction of gaze and visual sensitivity for two directions of eye rotation, leftward and rightward, before and after applying continuous theta burst stimulation (cTBS) over  $S1_{EYE}$  in healthy participants. cTBS decreases the excitability of the area underneath the coil when applied to the motor (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005) or the somatosensory (Ishikawa et al., 2007) cortices. We measured the effect of  $S1_{EYE}$ -cTBS on perceived eye position (indexed by the amplitude of the saccades from a lateral fixation point to a central auditory target, Experiment 1) as well as on visual sensitivity (indexed by the RT for visual discrimination, Experiment 2).

In a third experiment, we asked whether  $S1_{EYE}$ -cTBS also causes a lateral bias in visual exploration (Experiment 3). For instance in the posterior parietal cortex, a decrease

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of excitability of the right posterior parietal cortex with inhibitory rTMS not only increases visual sensitivity in the right hemifield (Hilgetag & Pascual-Leone, 2001) but also increases the time the participants spend looking in the right hemispace when viewing visual scenes (Nyffeler et al., 2008).

## METHODS

### Participants

All participants were healthy adults, right-handed by self-report, with normal, or corrected-to-normal vision. They gave written, informed consent to participate. The study was approved by the Ethics Committee of the Medical Department of the University of Tuebingen. For Experiment 1, 14 participants were tested: age median = 25 years, range = 20–28 years, 10 women. In Experiment 2, we tested 13 participants: age median = 28 years, range = 23–33 years, 7 women. For Experiment 3, we tested 12 participants: age median = 28.5 years, range = 23–33, 5 women. Two participants took part in all three experiments, five participants took part in Experiments 1 and 2, and three participants participated in Experiments 2 and 3.

### Tasks

All tasks were performed in right, monocular vision while the left eye was covered with a patch. The head was fixed in a chin rest using cheek pads. The position of the right eye was recorded.

### Experiment 1

This experiment investigated the effect of S1<sub>EYE</sub>-cTBS on perceived eye position by measuring the saccade amplitude from a lateral, visual fixation point to a central auditory target. As a control, a second condition where the target was presented in the visual rather than auditory modality was used. The main oculomotor structures such as the FEF (Russo & Bruce, 1994) or the superior colliculi (Jay & Sparks, 1984) code the direction of the saccade for both auditory and visual targets in an eye-centered reference frame. Saccades to visual targets can be planned in an eye-centered reference frame without information about eye position at saccade onset. In contrast, auditory targets are initially coded relative to the ears and the head. Therefore, knowledge of eye position is critical for planning saccades to sounds.

The participants sat in a completely dark room. An LED array was placed at 46 cm in front of them, with its center aligned to the head and body midline. LEDs indicated fixation points at 10° to the left or right as well as the visual target at 0° (straight ahead). The auditory target was a 100-msec burst of white noise presented in a small

speaker (diameter = 0.5 cm) attached to the LED array at 0° (Figure 1A, B). At the beginning of each trial the fixation LED was lit for 1100 msec. Then the target (LED or sound) was presented for 100 msec, then both target and fixation were turned off. The participant was instructed to move the eyes to the fixation LED and maintain fixation until both fixation and target were turned off, then to saccade to the location of the target. When ready for the next trial, the participant informed the experimenter, who started the next trial by pushing a button. Each run consisted of a block of 40 trials to the auditory target and 20 trials to the visual target. The order of visual and auditory blocks were identical within participants for both cTBS runs (pre- and post-cTBS) and stimulation sites (S1<sub>EYE</sub> and M1) and randomized across participants. Before the experiment, all participants underwent a practice run with eight trials per block. The training blocks were in the same order as the experiment blocks and were repeated until the participants performed at least 75% correctly timed saccades in each block.

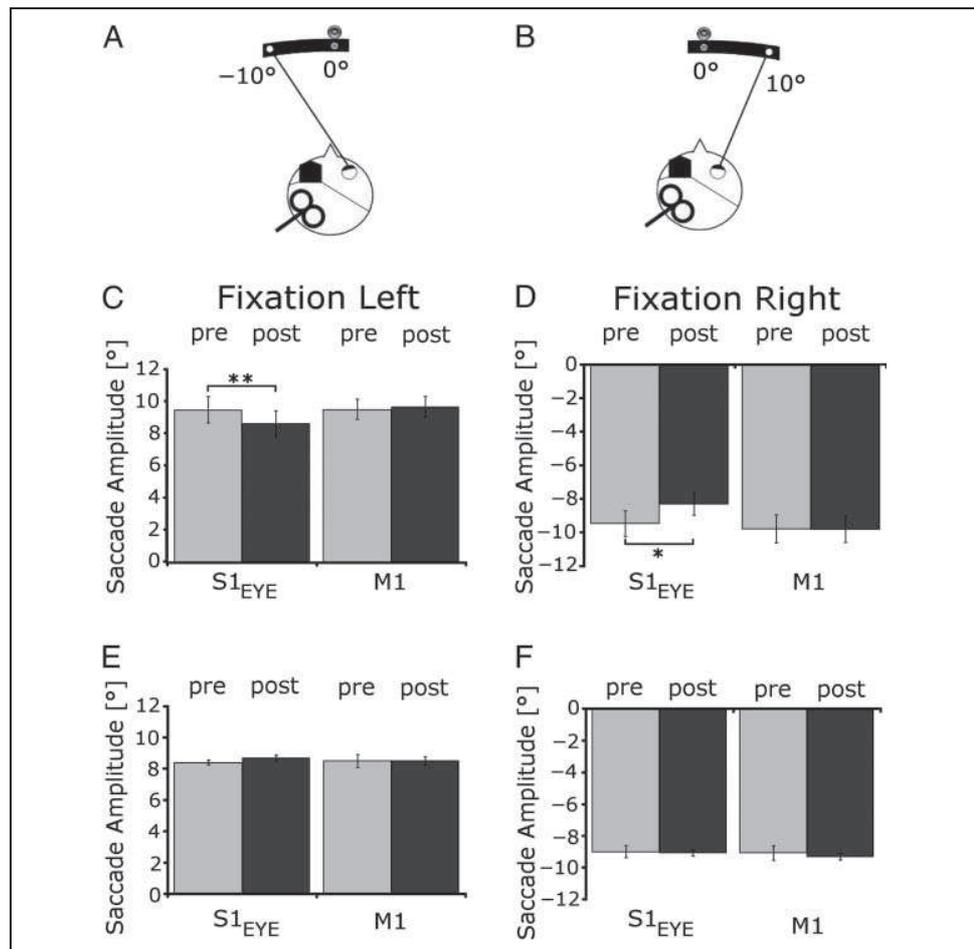
Data were analyzed with repeated-measure ANOVAs. Post hoc pairwise comparisons of the performance before and after cTBS were conducted using the Tukey's test. This test takes into account the multiple comparisons.

### Experiment 2

This experiment aimed to test whether S1<sub>EYE</sub>-cTBS causes lateral shifts in visual sensitivity. To this end, we attempted to replicate the observations of Balslev and colleagues (Balslev et al., 2011) using a TMS method and a setup that was consistent with Experiment 1. Thus, we used cTBS instead of 1-Hz rTMS and a setup where the gaze was maintained to the left or to the right, symmetrically relative to the orbit midline.

A computer screen was positioned with its center at  $\pm 14^\circ$  visual angle from the orbit midline of the right eye (Figure 2A, B). At the start of the trial, a fixation cross ( $1^\circ \times 1^\circ$ ) was presented at the center of the screen ( $14^\circ$  left or right from orbit center) for a randomized time interval between 1600 and 2400 msec. Then a target letter ("A" or "H,"  $1^\circ \times 1^\circ$ ) appeared for 120 msec at  $10^\circ$  visual angle to the left or to the right of the screen center. The participant was instructed to fixate the cross and respond as fast as possible to indicate the letter. To respond, he or she pressed with the left hand one of the two buttons of the response box ("A" or "H"). The participant had 2000 msec to respond before the start of a new trial. We measured the RT from target onset until button press as an index for visual sensitivity. RT for visual stimuli decreases with increasing stimulus luminance (Jaskowski, Rybarczyk, Jaroszyk, & Lemanski, 1995) and is therefore an adequate measure for visual sensitivity. Each participant completed 160 trials: the first 80 with the screen on one side and the last 80 trials with the screen on the other side. The order of the two gaze conditions (leftward, rightward) was counterbalanced across participants. Within each gaze

**Figure 1.** Shift in perceived eye position toward orbit midline after S1<sub>EYE</sub>-cTBS. Participants sat head-fixed in darkness with their left eye patched, fixating an LED at either  $-10^\circ$  (A) or  $+10^\circ$  (B) from body midline, so that the right eye was rotated leftward or rightward (continuous line). A saccade target, an LED or a sound burst, was presented at  $0^\circ$  (straight ahead) and extinguished before the onset of the eye movement. S1<sub>EYE</sub>-cTBS shortened the saccades to auditory targets (C–D), while leaving the saccades to visual targets unchanged (E–F). This reduction in saccade amplitude was specific to the stimulation site S1<sub>EYE</sub> and did not occur after M1-cTBS.  $n = 14$  participants, values with standard error of mean.  $**p < .01$ , using Tukey’s test.



condition, there were 20 trials for each letter and side of target presentation. The four different types of trials were intermixed in a pseudorandomized order. Before the experiment started, each participant underwent a practice run with 30 trials. To verify fixation, we recorded eye position.

Data were analyzed with repeated-measure ANOVAs. Post hoc pairwise comparisons of the performance before and after cTBS were conducted using Tukey’s tests. These tests took into consideration all pairwise comparisons for each side of the stimulus display.

### Experiment 3

To investigate the pattern of exploratory eye movements during visual search, participants were instructed to look for the letter “A” within a letter array (height  $\times$  width,  $50^\circ \times 25^\circ$ ). The array was presented laterally at  $14^\circ$  visual angle to the left or to the right of the center of the right orbit so that, to fixate any letter within the array, the eye had to be rotated leftward or rightward, respectively (Figure 3A, B). Each array showed randomly distributed black capital letters from B to Z ( $1^\circ$  visual angle, 113 letters in the left and 119 letters in the right array). Each

letter was printed on a separate piece of white paper, attached to the array. Unbeknownst to the participants, the letter “A” was absent from the array. This paradigm for investigating the exploratory, spontaneous eye movements during visual search was adapted from Karnath and colleagues (Karnath, Niemeier, & Dichgans, 1998). Before the trial, the arrays were covered. At the beginning of the trial, the cover was removed and the participants instructed to search one lateral array. Eye movements were recorded for 20 sec, then the array was again covered. The mean gaze position during this search was calculated and compared across conditions.

Data were analyzed with repeated-measure ANOVAs. Post hoc pairwise comparisons of the performance before and after cTBS were conducted using Tukey’s tests, which took into consideration all pairwise comparisons for each side of the letter array. To keep the participants motivated, in a practice trial before the experiment, a letter A was attached at the center of the left array. If the participant did not find the target within 20 sec, the experimenter identified its location by pointing to it. This was the case in one participant. Each participant completed two trials of 20-sec duration, one for each lateral array (leftward and rightward).

## Eye Tracking

The position of the right eye was recorded with a head-mounted tracker (EYELINK II, SR Research Ltd., Ottawa, Canada) that sampled pupil location at 250 Hz. The tracker was calibrated after each cTBS run (pre- or post-cTBS) and for each lateral position of the screen (Experiment 2) or array (Experiment 3) using a horizontal grid (Experiment 1) or a 3 × 3 grid (Experiments 2 and 3).

Eye position time series were parsed into fixations, blinks, and saccades using the SR EyeLink detection algorithm, which was set to detect saccades with an amplitude of at least 0.5°, using an acceleration threshold of 9500/sec<sup>2</sup> and a velocity threshold of 30/sec, and then analyzed off-line. To assess the effect of cTBS on calibration, we compared its accuracy and precision between the pre- and post-cTBS runs using paired *t* test. Calibration accuracy was indexed by the signed error between the position of the calibration point and the eye position returned by the calibration algorithm. Precision was measured by the standard deviation of this error.

For Experiment 1, trials with anticipatory saccades, performed before the target was extinguished, were discarded. For the remaining trials, we calculated the amplitude of the first saccade after the target was turned off. In addition, to investigate whether S1<sub>EYE</sub>-cTBS changed the initial eye position during fixation, we compared eye position averaged over 200 msec of fixation before saccade onset across con-

ditions (pre- vs. post-cTBS) using paired *t* tests. To assess the effect of cTBS on the ability to plan and execute saccades, we compared saccade velocity and RT until saccade onset between the two cTBS runs (pre- vs. post-cTBS).

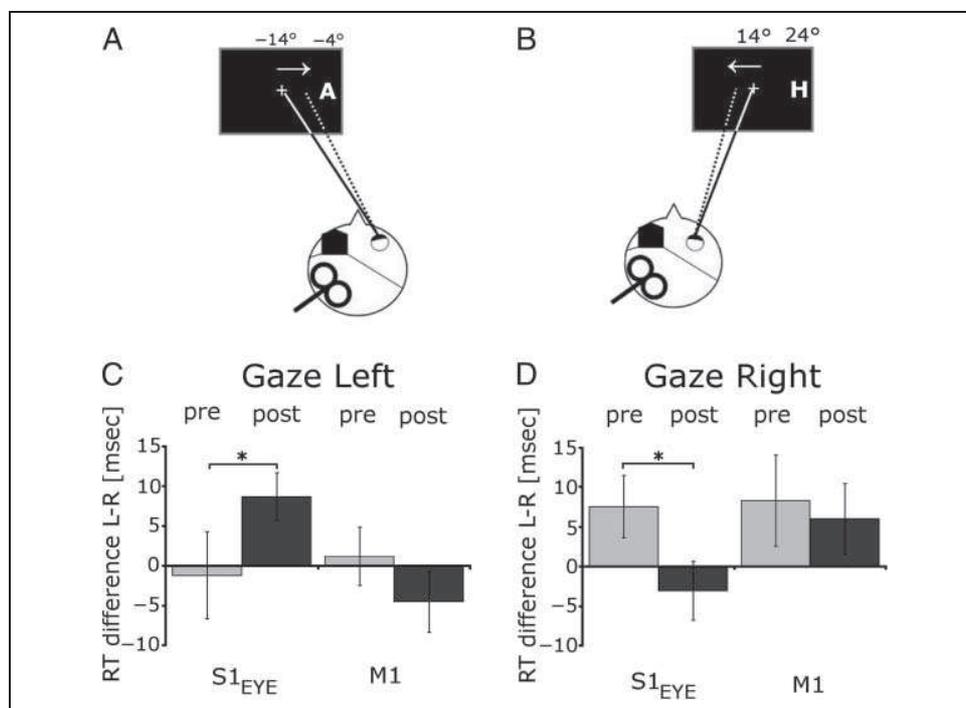
For Experiment 2, mean gaze position was calculated for a 200-msec interval before the target onset. Trials with a gaze deviation of more than 1° from the fixation cross were discarded. To investigate whether cTBS caused a lateral bias in the spontaneous eye movements, we calculated the amplitude and frequency of incidental saccades during required fixation and submitted them to the same repeated-measures ANOVA as the RT data.

For Experiment 3, blinks were excluded, and then mean eye position during visual search was calculated. To investigate whether changes in mean eye position were caused by lateralized changes in the fixation time or the amplitude or frequency of the saccades, these parameters were calculated and compared across conditions using repeated-measures ANOVAs and Tukey's tests.

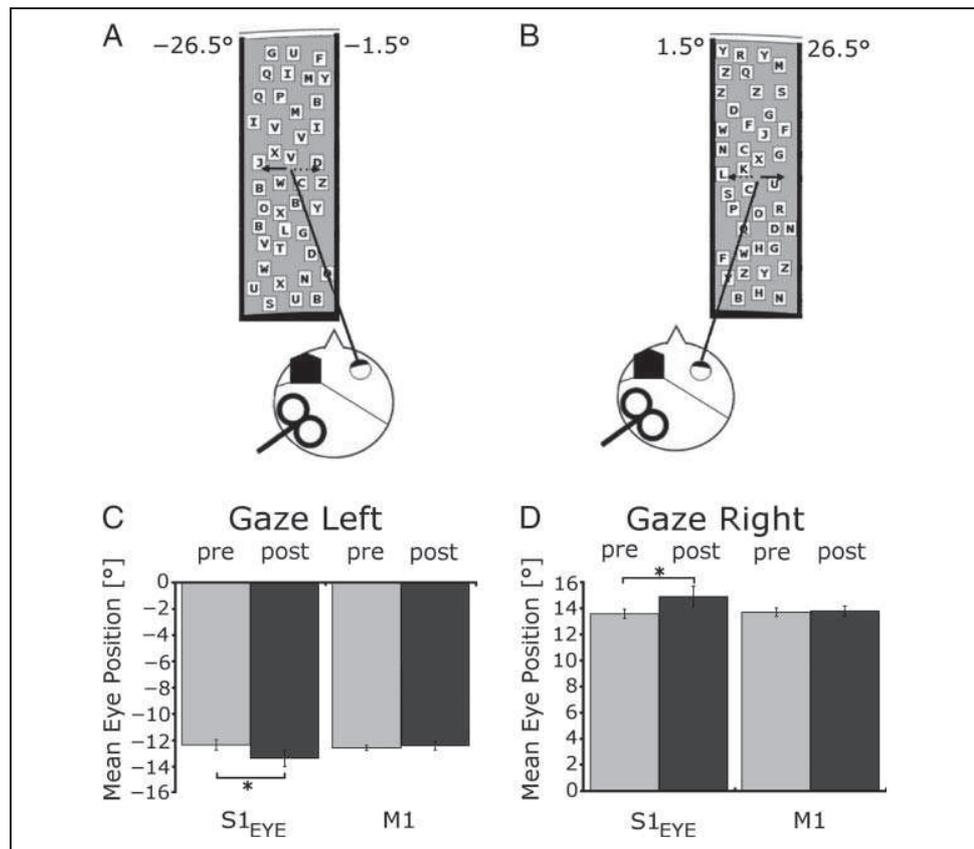
## TMS

A standard 70-mm-diameter figure-of-eight coil centered over the stimulation site was fixed in place by a coil holder. The participant's head was restrained by a chin rest. We followed an identical procedure for locating the eye proprioceptive area as in previous studies, conducted by

**Figure 2.** Increase in visual sensitivity toward orbit midline after S1<sub>EYE</sub>-cTBS. In right eye vision participants fixated at ±14° to the left (A) or right (B) from the center of the orbit. A target letter, "A" or "H" was presented for 120 msec in the left or right hemifield at 10°. The continuous line (A–B) shows the actual direction of gaze at fixation and the dashed line shows the perceived direction of gaze according to the results of Experiment 1. After S1<sub>EYE</sub>-cTBS, the gradient in RT between the left minus right hemifield increased in leftward gaze showing a perceptual advantage for right hemifield targets (C) and decreased in rightward gaze, showing an advantage for left hemifield targets (D). The arrow (A–B) shows the direction of the increase in visual sensitivity, in the same direction as the shift in perceived eye position during Experiment 1. L, left; R, right, *n* = 13 participants, values with standard error of mean. \**p* < .05, using Tukey's test.



**Figure 3.** Mean gaze during visual search shifts away from orbit midline after S1<sub>EYE</sub>-cTBS. Participants searched for a nonexistent letter A in a 25°-wide array centered at 14° to the left and right of the orbit center of the right eye so that the gaze (continuous line) was rotated leftward (A) or rightward (B) when fixating any element of the array. The dashed arrow shows the direction of the increase in visual sensitivity according to the results of Experiment 2. After S1<sub>EYE</sub>-cTBS, mean eye position shifted to the left during search in the leftward array (C) and to the right during search in the rightward array (D). The continuous arrow (A–B) shows the direction of this shift in mean gaze position. The shift was specific to the stimulation site in S1<sub>EYE</sub> and did not occur after M1-cTBS. *n* = 12 participants, values with standard error of mean. \**p* < .05, using Tukey’s test.



Balslev and colleagues (Balslev et al., 2011; Balslev & Miall, 2008). S1<sub>EYE</sub> was mapped in each participant in relation to the “motor hotspot” of the left hemisphere, which is the scalp projection of the primary motor cortex for the hand (M1). The motor hotspot was defined as the point of maximum evoked motor response in the first dorsal interosseus muscle of the right hand. The S1<sub>EYE</sub> site of stimulation was located at 3 cm posterior to the motor hotspot, measured on a line oriented at 45° from the sagittal plane and perpendicular on the central sulcus. Post hoc neuronavigation has showed that this coil location targets the postcentral gyrus (Figure 2 in Balslev, Siebner, et al., 2012). During stimulation, the coil was positioned tangential to the scalp with the long axis of the figure-of-eight coil oriented at 45° to the parasagittal plane. The current flow of the initial rising phase of the biphasic pulse in the TMS coil induced a current flowing from posterior to anterior in the brain. On the basis of the decreased amplitude of the somatosensory-evoked potentials after cTBS over a region situated at 2 cm posterior to M1 (Ishikawa et al., 2007), we assumed that cTBS over S1<sub>EYE</sub> results in a decreased excitability of this area. The control site of stimulation M1 was located at the motor hotspot for the right hand. The choice of this control area was motivated by our previous TMS studies showing no effect of inhibitory TMS at this site on either visual localization (Balslev & Miall, 2008) or visuospatial attention (Balslev et al., 2011).

Each cTBS consisted of 600 biphasic stimuli produced by a Magstim Rapid<sup>2</sup> stimulator. They were delivered with a frequency of three pulses at 50 Hz repeated at 200 msec (5 Hz) for 40 sec. The stimulation intensity was set at 80% of active motor threshold of the right first dorsal interosseus (Huang et al., 2005). For each experiment, participants underwent two sessions, with cTBS at either S1<sub>EYE</sub> or the control site (M1). The order of the sessions was randomized across participants and scheduled on separate days. During each session, the participant was tested before (pre-cTBS) and after (post-cTBS) on an identical task. Data collection was completed within 13 min after the cessation of the stimulation, a time interval for which the inhibitory aftereffect of cTBS in the somatosensory cortex has been demonstrated (Ishikawa et al., 2007). To prevent a potential recalibration of eye position by vision (Duke, Oruç, Qi, & Backus, 2006), participants were instructed to keep their eyes closed while receiving cTBS and until the start of the post-cTMS run.

## RESULTS

### Experiment 1

This experiment investigated whether cTBS over the somatosensory cortex causes an underestimation of the rotation of the eye in the orbit. We predicted that S1<sub>EYE</sub>-

cTBS would reduce the amplitude of the saccades from a lateral fixation point to a central auditory target. Because saccades to visual targets can be planned in retinotopic coordinates without information about eye position, no effect of S1<sub>EYE</sub>-cTBS on the amplitude of the visually guided saccades was expected.

A total of  $16.18 \pm 8.90\%$  (mean  $\pm$  standard deviation) trials were discarded because of anticipatory saccades, which started before the target was extinguished. As predicted, after S1<sub>EYE</sub>-cTBS, saccades from a lateral fixation to a central auditory were  $\sim 1$  degree shorter compared with the pre-cTBS and the M1-cTBS control, causing errors to the left for leftward fixation and to the right for rightward fixation (Figure 1C–F). Indeed for leftward eye rotation at the saccade onset, the amplitude of the saccades was  $9.45^\circ \pm 3.15^\circ$  before and  $8.59^\circ \pm 3.01^\circ$  after cTBS. For rightward eye rotation, the corresponding values were  $9.48^\circ \pm 2.20^\circ$  pre-cTBS and  $8.32^\circ \pm 1.94^\circ$  post-cTBS (pairwise comparisons using Tukey's test, both  $p < .05$ ). The reduction in saccade amplitude post-cTBS versus pre-cTBS was specific for S1<sub>EYE</sub> and the auditory targets. None of the other comparisons (e.g., for M1-cTBS or for visual targets) were statistically significant (all  $ps > .05$ ).

The repeated-measures ANOVA with factors (1) Target Modality (visual or auditory), (2) Stimulation Site (M1 or S1<sub>EYE</sub>), (3) cTBS Run (pre- or post-cTBS), and (4) Side of Saccades (left or right) showed a significant four-way interaction,  $F(1, 13) = 9.452, p = .009$ . A significant interaction could be found between Modality  $\times$  Run  $\times$  Side of Saccades,  $F(1, 13) = 13.09, p = .003$ . Further analyses (three-way ANOVAs with factors Modality  $\times$  Run  $\times$  Side of Saccades ran separately for S1<sub>EYE</sub>-cTBS and M1-cTBS data) showed a significant three-way interaction in the S1<sub>EYE</sub>-cTBS only (S1<sub>EYE</sub>-cTBS,  $F(1, 13) = 24.88, p < .001$ ; M1-cTBS:  $F(1, 13) = 0.006, p = .94$ ). None of the other main effects or interactions was significant.

We found no evidence that S1<sub>EYE</sub>-cTBS interferes with the participants' ability to fixate. The repeated-measures ANOVA for initial eye position data showed no significant three-way interaction between Stimulation Site  $\times$  cTBS Run  $\times$  Side of Saccades for either visual or auditory targets (both  $p > .53$ ). Likewise, post hoc pairwise comparisons using the Tukey's test showed no significant difference of initial eye position pre-cTBS versus post-cTBS in either condition (M1-cTBS or S1<sub>EYE</sub>-cTBS for visual or auditory targets).

Furthermore, the effect of S1<sub>EYE</sub>-cTBS was specific to the amplitude of the saccades and did not extend to other measures of saccade kinematics. The analysis of saccade velocity or RT until saccade onset showed no significant effect of cTBS at either stimulation site and for either of the two modalities of the target (ANOVAs with factors Stimulation Site  $\times$  cTBS Run  $\times$  Side of Stimulation for saccade velocity and RT for both modalities: all  $ps > .261$  for main effects and interactions).

The reduction in amplitude of the saccades to auditory targets after S1<sub>EYE</sub>-cTBS indicated an error in saccade planning caused by an underestimation of the rotation of the

eye in the orbit. S1<sub>EYE</sub>-cTBS can thus dissociate the real direction of gaze from the perceived direction of gaze. Thus, it provides a method to investigate whether changes in perceived eye position are associated with changes in visual sensitivity.

## Experiment 2

Experiment 2 used the cTBS method to investigate for a lateral change in visual sensitivity. To this end, we measured RTs for discriminating briefly presented letters in the left and right visual hemifield in leftward or rightward gaze. If visual sensitivity shifts in the same direction as perceived eye position does, S1<sub>EYE</sub>-cTBS should speed up the discrimination of the letters located nearer the orbit center (in the left visual hemifield in rightward gaze and in the right visual hemifield for leftward gaze).

Trials with a break of fixation were discarded ( $8.53 \pm 3.13\%$ ). In accord with the prediction, S1<sub>EYE</sub>-cTBS (but not M1-cTBS) changed the left–right gradient in the RT for letter discrimination to favor locations nearer the center of the orbit (Figure 2C, D). That is, in leftward gaze, the difference in RT for left minus right targets increased (Figure 2C, pre-S1<sub>EYE</sub>-cTBS:  $1.22 \pm 19.64$  msec, post-S1<sub>EYE</sub>-cTBS:  $16.33 \pm 25.26$  msec, post hoc pairwise comparisons, Tukey's test,  $p < .05$ ). In rightward gaze, the difference in RT for left minus right targets decreased (Figure 2D, pre-S1<sub>EYE</sub>-cTBS:  $7.53 \pm 14.09$  msec, post-S1<sub>EYE</sub>-cTBS:  $-3.07 \pm 13.31$  msec, Tukey's test,  $p < .05$ ). Similar pairwise comparisons for the RTs after M1-cTBS showed no statistically significant (all  $ps > .05$ ). The repeated-measures ANOVA with factors (1) Stimulation Site (S1<sub>EYE</sub> or M1), (2) cTBS Run (pre-cTBS or post-cTBS), (3) the Direction of Rotation of the Right Eye (leftward or rightward), and (4) Visual Hemifield in which the target letter appeared (left or right) showed a significant four-way interaction,  $F(1, 12) = 13.58, p = .003$ . A significant interaction was also found between Stimulation Site  $\times$  the Direction of Rotation of the Right Eye  $\times$  Target Side,  $F(1, 12) = 6.474, p = .023$ . This interaction was driven by post-cTBS data. Three-way ANOVAs (Stimulation Site  $\times$  Direction of Rotation of the Right Eye  $\times$  Target Side) was significant for post-cTBS-data,  $F(1, 12) = 16.996, p = .001$ , but not pre-cTBS data,  $F(1, 12) = 0.112, p = .74$ . No other main effects or interactions were found in any of the ANOVAs.

Discrimination accuracy over all participants and conditions approached ceiling ( $94.52 \pm 5.07\%$ ) with no significant difference between conditions (repeated-measures ANOVA, four-way interaction,  $F(1, 12) = 0.605, p > .45$ ). We found a nonsignificant trend ( $p = .094$ ) for an interaction between stimulation site and eye rotation, which is irrelevant for the tested hypothesis. We failed to find any other statistical significant main effect or interaction (all  $ps > .15$ ).

In contrast with the RT for letter discrimination, the analysis of incidental saccades showed no statistically significant

spatial bias in the eye movements after S1<sub>EYE</sub>-cTBS. The four-way interaction was not significant for either the amplitude,  $F(1, 12) = 1.227, p = .29$ , or for the frequency,  $F(1, 12) = 0.334, p = .57$ , of these incidental saccades. No significant main effects or interactions were found.

The results of Experiment 2 confirmed the hypothesis that S1<sub>EYE</sub>-cTBS shifted visual sensitivity toward the center of the orbit, in the same direction as the shifts in perceived eye position (Experiment 1). We wondered whether this reflects a more general bias for the space nearer the center of the orbit, for instance, whether in addition to the increase in visual sensitivity, the exploratory eye movements too will show a preference toward this space.

### Experiment 3

To investigate whether S1<sub>EYE</sub>-cTBS causes a lateral shift in the exploratory eye movements, participants performed a visual search task in lateral letter arrays while their gaze position was recorded.

We found that after S1<sub>EYE</sub>-cTBS mean gaze during visual search was shifted  $\sim 1^\circ$  away from the orbit midline, that is to the left during visual search in the leftward letter array (pre-S1<sub>EYE</sub>-cTBS:  $-12.35 \pm 1.4^\circ$ , post-S1<sub>EYE</sub>-cTBS:  $-13.36 \pm 2.21^\circ$ , post hoc pairwise multiple comparison using Tukey's test,  $p < .05$ ; Figure 3C) and to the right for the rightward array (pre-S1<sub>EYE</sub>-cTBS:  $13.57 \pm 1.28^\circ$ , post-S1<sub>EYE</sub>-cTBS:  $14.91 \pm 2.77^\circ$ , post hoc pairwise multiple comparison using Tukey's test  $p < .01$ ; Figure 3D). This effect was specific to S1<sub>EYE</sub>-cTBS. After M1-cTBS, there was no statistically significant difference in mean gaze position during visual search in either array. The repeated-measures ANOVA with factors (1) Stimulation Site (S1<sub>EYE</sub> or M1), (2) cTBS Run (pre-cTBS or post-cTBS), and (3) the Side of the Array (left or right) showed a statistically significant three-way interaction,  $F(1, 11) = 17.66, p = .001$ . A significant main effect was found for eye rotation,  $F(1, 11) = 1507.51, p < .001$ . This main effect can be explained by the different direction of eye rotation for each array, giving negative values for rotation to the left and positive values for rotation to the right. None of the other main effects and no interactions were significant.

The shift in mean eye position after cTBS was caused by an increase in the fixation time in the "outer" half of the array (the half of the array located further from the orbit midline), rather than by an increase in the amplitude or the frequency of the saccades in that direction. Indeed, S1<sub>EYE</sub>-cTBS increased the left minus right gradient in the fixation time for the left array (pre-S1<sub>EYE</sub>-cTBS:  $-4.08 \pm 2.46$  sec, post-S1<sub>EYE</sub>-cTBS:  $-1.78 \pm 3.14$  sec, post hoc pairwise comparisons, Tukey's test,  $p < .05$ ). In the right array, the left minus right gradient shifted toward the right half of the array (pre-S1<sub>EYE</sub>-cTBS:  $1.68 \pm 2.54$  sec, post-S1<sub>EYE</sub>-cTBS:  $-0.68 \pm 1.66$  sec, Tukey's test,  $p < .05$ ). Similar pairwise comparisons for fixation time after M1-cTBS showed no statistically significant difference (pre-M1-cTBS for left array:  $-3.01 \pm 2.77$  sec, post-M1-cTBS for left array:

$-4.34 \pm 3.21$  sec; pre-M1-cTBS for right array:  $0.94 \pm 3.05$  sec, post-M1-cTBS for left array:  $1.04 \pm 3.12$  sec; all  $ps > .05$ ). The full four-way ANOVA conducted on fixation time data with factors (1) Stimulation Site (S1<sub>EYE</sub> or M1), (2) cTBS Run (pre-cTBS or post-cTBS), (3) the Side of the Array (leftward or rightward), and (4) the Half of the Array where the Fixation Fell (left or right) showed a statistically significant four-way interaction,  $F(1, 11) = 13.973, p = .003$ . A similar ANOVA performed on the number of fixations showed no statistically significant main effects or interactions (all  $ps > .12$ ).

In contrast to the fixation time, the amplitude and frequency of the saccades showed no statistically significant interaction between Stimulation Site  $\times$  cTBS Run  $\times$  Array Side  $\times$  Saccade Direction (left or right),  $F(1, 11) = 0.048, p > .83$  for amplitude and  $F(1, 11) = 0.097, p > .76$  for frequency. No other main effects or interactions were statistically significant.

Experiment 3 showed a shift in mean eye position and longer fixation time further from the orbit midline in opposite direction to the shift in visual sensitivity (Experiment 2). This did not support the hypothesis that S1<sub>EYE</sub>-cTBS causes a spatial bias that generalizes from visual sensitivity to visual exploration.

### cTBS Effects on Calibration

Neither calibration accuracy nor precision were affected by cTBS. The mean calibration error was below  $0.01^\circ$  for either experiment (1, 2, or 3), cTBS run (pre- or post-cTBS) or stimulation site (M1 or S1<sub>EYE</sub>). The standard deviation of this error was below  $2.56^\circ$ . For each of the three experiments, paired-samples *t* tests showed no statistically significant difference between pre- and post-cTBS for either stimulation site (all  $ps > .11$ ).

### DISCUSSION

Experiment 1 showed that S1<sub>EYE</sub>-cTBS affected the amplitude of the saccades from a lateral, left or right eye rotation to a central auditory, but not visual target. We argue that the size of the saccade to auditory targets reflects the perceived eye position at the onset of the saccade. Our argument is based on the preferential coding of both auditory and visual saccade targets in eye-centered coordinates at the level of the superior colliculus (Jay & Sparks, 1984) and FEF (Russo & Bruce, 1994). Because the brain extracts the location of the auditory stimuli relative to the ears and the head, saccades to auditory targets critically depend on information of eye position to transform head- into eye-centered representations.

These changes in the perceived eye position were triggered from the same brain area (S1<sub>EYE</sub>) where we have previously demonstrated an afferent projection from the eye muscles (Balslev & Miall, 2008). Neuronavigation has placed this area in the left postcentral gyrus (Balslev, Siebner, et al., 2012). For both leftward and rightward eye

position at fixation, S1<sub>EYE</sub>-cTBS caused an undershoot of the auditory-guided saccades. This suggests an underestimation of the rotation of the eye in the orbit at fixation. This effect can be predicted under two assumptions. First, we assumed that the human eye proprioceptive area S1<sub>EYE</sub> (Balslev & Miall, 2008) is organized like the proprioceptive area 3a identified in the macaque. In the macaque area 3a, the frequency of neural firing increases with the rotation of the eye in the orbit for all gaze directions (Wang et al., 2007). If the eye proprioceptive area in the human brain codes the angle of gaze in the same way, a decrease of excitability of this neuronal population would decrease in neuronal firing for a given angle of eye rotation and cause an underestimation of this angle. Second, we assumed that cTBS over S1<sub>EYE</sub> causes a decrease of excitability of this area. cTBS has been shown to decrease cortical excitability of the area underneath the coil (Huang et al., 2005). In particular, when applied at 2 cm posterior to M1, cTBS decreases the amplitude of the somatosensory-evoked potentials (Ishikawa et al., 2007), which is a correlate of the cortical excitability in the somatosensory cortex.

The absence of a statistically significant effect on saccades to visual targets on the initial position at fixation as well as on other measures of saccade kinematics (velocity and time until onset) rules out a general effect of S1<sub>EYE</sub>-cTBS on the ability to fixate or to execute saccades.

In Experiment 2, we have used S1<sub>EYE</sub>-cTBS as a method to dissociate perceived gaze direction from actual gaze direction to investigate its association with a spatially congruent shift in visual sensitivity. In line with this hypothesis, we found that S1<sub>EYE</sub>-cTBS indeed caused a decrease in the RTs for discriminating a letter when the letter was presented nearer the orbit midline. The increase in visual sensitivity toward orbit midline observed here in the RT measures was consistent with that found in visual accuracy (Balslev et al., 2011) as well as with the variation in the extrastriate cortex neural activity (Balslev, Siebner, et al., 2012) after 1-Hz rTMS in S1<sub>EYE</sub>.

Experiment 3 did not support the hypothesis that S1<sub>EYE</sub>-cTBS cause a lateral bias in visual exploration in the same direction as the increase in visual sensitivity. When participants searched a lateral array, S1<sub>EYE</sub>-cTBS shifted mean eye position away from the orbit midline, in opposite direction as the increase in visual sensitivity. This shift in mean eye position was caused by an increased fixation time in the half of the array that was further from the orbit midline. One could attempt to explain the direction of this shift in two ways. First, stimulus visibility is a well-established factor that influences oculomotor behavior during visual search (Najemnik & Geisler, 2005; Näsänen, Ojanpää, & Kojo, 2001; Jacobs & O'Regan, 1987). Humans adapt their saccades and fixations to the visibility of the array to optimize the time needed to find the target (Najemnik & Geisler, 2005). After S1<sub>EYE</sub>-cTBS, participants have lower visual sensitivity for the area of the array located further from the orbit midline. Fixating toward the outer regions of the array would bring

the area of low visibility closer to the fovea. An alternative to this explanation is that the shift in mean eye position during visual search away from the orbit midline does not reflect the asymmetric visual sensitivity, but rather the shift in perceived gaze position. For instance, the participants may have perceived their gaze as being closer to the center of the array than it actually was. It is currently not known whether the oculomotor behavior during visual search is directly affected by the eye proprioceptive information. We believe this explanation is less likely, given that S1<sub>EYE</sub>-cTBS did not interfere with the participants' ability to fixate or to execute saccades under visual guidance (Experiment 1).

The results of the first two experiments show that the lateral shift in visual sensitivity induced by changing the excitability of S1<sub>EYE</sub> is spatially congruent with the rTMS-induced shift in perceived gaze direction. This spatial congruence lends support to the hypothesis that the eye proprioceptive area in the somatosensory cortex plays a role in visuospatial attention. S1<sub>EYE</sub>-cTBS increased visual sensitivity in the display area located nearer the orbit midline (Experiment 2) and shifted mean eye position during visual exploration in the opposite direction toward the area of the array located further from the body midline (Experiment 3). The spatially incongruent effects on visual sensitivity and visual exploration do not support an interpretation of the role of S1<sub>EYE</sub> in terms of visual orienting (a bias in both visual sensitivity and oculomotor behavior in the same direction). The null result when we tested for a lateral gradient in the amplitude or frequency of the incidental saccades in Experiment 2 is in line with this interpretation.

Visual sensitivity increased nearer to the orbit midline compared with further from orbit midline, although stimuli were presented at equal retinal eccentricity (Experiment 2). We argue that this difference in visual sensitivity reflects the effect of S1<sub>EYE</sub>-cTBS on visuospatial attention. Spatial attention can be defined as the selection of a location for privileged stimulus processing (Petersen & Posner, 2012; Bisley & Goldberg, 2010). The change in visual sensitivity for retinally identical stimuli has previously been interpreted as a signature of the neural processes that implement this function (Ruff et al., 2006; Cavanaugh & Wurtz, 2004; Moore & Fallah, 2004; Hilgetag & Pascual-Leone, 2001). To the best of our knowledge, spatial attention is implemented by a network that, at cortical level, consists of the FEF, areas around the intraparietal sulcus, the TPJ, and the ventral frontal cortex (Petersen & Posner, 2012; Bisley & Goldberg, 2010; Corbetta & Shulman, 2002). The current results point to the somatosensory cortex as an additional node in this network.

Because the rTMS-induced electric field can spread both locally to the adjacent areas as well as remotely, through neural connections, one could object that the effects on visual sensitivity reported here do not arise from the area underneath the coil but rather from the parieto-premotor areas, which are located near the somatosensory cortex and are likely to be interconnected with it.

Against this interpretation speaks the difference between the current results and the findings of previous studies, in which TMS was applied directly over the posterior parietal cortex or the FEF. For instance, inhibitory rTMS applied at the posterior parietal foci P3/P4 can enhance the perception of stimuli located in the visual hemifield ipsilateral to the hemisphere where rTMS was applied (Hilgetag & Pascual-Leone, 2001) or bias visual exploration (i.e., fixation time) toward the hemispace located contralateral to the rTMS site (Nyffeler et al., 2008). This effect differs from the rTMS effects observed here. After S1<sub>EYE</sub>-cTBS, the RT for detecting a target as well as the mean gaze position during visual search did not show a simple dependence on the visual hemifield or the body/head hemispace but rather an interaction between these two factors. Namely, after S1<sub>EYE</sub>-cTBS a right hemifield target was detected more accurately than a left one only when both targets were presented to the left of the body/head midline, whereas to the right of the body/head midline the results were reversed. Applied over the FEF, TMS can also affect visual sensitivity. However, the variation in visual sensitivity depends on the eccentricity of the stimulus on the retina, for example, increased in the periphery compared with the center (Ruff et al., 2006). This again differs from the results reported here. Therefore, we argue that the variation in visual sensitivity after S1<sub>EYE</sub>-cTBS is unlikely to have been caused merely by a spread of the induced electric field to these areas, whose function in visuospatial attention is well established.

## Conclusion

The current study demonstrated that visual sensitivity increases in the direction of the perceived gaze. We suggest therefore that the cortical eye position signal in the somatosensory cortex and visuospatial attention are functionally coupled. The resolution of the TMS method does not allow to conclude whether the neural population responsible for the change in visual sensitivity colocalizes with that coding the direction of gaze. However, this speculation seems to us reasonable, given that the changes in visuospatial attention were elicited from the same TMS coil placement that targets the human eye proprioceptive area (Balslev & Miall, 2008). We anticipate therefore that this finding will fuel further research into the role of the recently discovered eye proprioceptive area in visuospatial attention by exploring its anatomical connectivity and its functional interdependence with other nodes of the spatial attention network.

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# Role of Somatosensory Cortex in Visuospatial Attention

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The human somatosensory cortex (S1) is not among the brain areas usually associated with visuospatial attention. However, such a function can be presumed, given the recently identified eye proprioceptive input to S1 and the established links between gaze and attention. Here we investigated a rare patient with a focal lesion of the right postcentral gyrus that interferes with the processing of eye proprioception without affecting the ability to locate visual objects relative to her body or to execute eye movements. As a behavioral measure of spatial attention, we recorded fixation time during visual search and reaction time for visual discrimination in lateral displays. In contrast to a group of age-matched controls, the patient showed a gradient in looking time and in visual sensitivity toward the midline. Because an attention bias in the opposite direction, toward the ipsilesional space, occurs in patients with spatial neglect, in a second study, we asked whether the incidental coinjury of S1 together with the neglect-typical perisylvian lesion leads to a milder neglect. A voxelwise lesion behavior mapping analysis of a group of right-hemisphere stroke patients supported this hypothesis. The effect of an isolated S1 lesion on visual exploration and visual sensitivity as well as the modulatory role of S1 in spatial neglect suggest a role of this area in visuospatial attention. We hypothesize that the proprioceptive gaze signal in S1, although playing only a minor role in locating visual objects relative to the body, affects the allocation of attention in the visual space.

## Introduction

Visuospatial attention can be defined as the selection of a location in the visual space for preferential stimulus processing. Previous research has associated this function with a network in the higher-order frontal, parietal, and temporal cortices and subcortical structures, such as thalamus and superior colliculi (Corbetta and Shulman, 2002; Bissley and Goldberg, 2010; Karnath and Rorden, 2012; Petersen and Posner, 2012). The primary somatosensory cortex (S1) is not among these areas. However, a role of S1 in visuospatial attention can be presumed, given its recently discovered proprioceptive gaze input (Wang et al., 2007; Balslev and Miall, 2008) and the established links between gaze and attention. First, many oculomotor areas, such as the superior colliculi or the frontal eye fields, have an additional function in spatial attention. For instance the coinjury of the superior colliculus (Sprague, 1966; Weddell, 2004) or the frontal eye field (Vuilleumier et al., 1996) can alleviate spatial neglect. Second, to stabilize the focus of attention across eye movements or to allow cross-modal interactions in spatial attention, locations must be coded in non-retinotopic coordinates (Andersen et al., 1985;

Galletti et al., 1993) or updated across eye movements (Duhamel et al., 1992). These processes require gaze information. Eye proprioception, as well as the efference copy of the oculomotor command, provide such information and could thus be used for coding the locus of attention.

To investigate whether S1 plays a role in visuospatial attention, here we conducted two studies in brain-lesioned patients. Study 1 examined a patient with a rare circumscribed stroke in the right postcentral gyrus. This patient has a deficit in processing proprioceptive input from the left, contralesional, eye. Her ability to locate visual objects relative to the body was normal, presumably by relying exclusively on the efference copy of the motor command (Balslev et al., 2012a). We recorded the patient's fixation time during visual search in lateral, left and right, letter arrays (Experiment A) as well as the reaction time for discriminating left- and right-hemifield targets presented at equal retinal eccentricity in lateral left and right displays (Experiment B). The setup with lateral visual displays was guided by our previous work. After inhibitory repetitive transcranial magnetic stimulation (rTMS) over S1, both perceived gaze and the locus of attention shift toward the midline, that is to the left in rightward gaze and to the right in leftward gaze (Odoj and Balslev, 2013). Therefore, we hypothesized that an isolated S1 stroke would cause a bias in visual search that depends on the direction of gaze (Study 1). Study 2 asked whether the coinjury of S1 exerts a modulatory effect on the ipsilesional selection bias in spatial neglect. Patients with spatial neglect, usually after a right perisylvian lesion (Karnath and Rorden, 2012), show a lateral bias during visual search (Hornak, 1992; Karnath, 1994; Karnath et al., 1998). The prediction of a modulatory effect of an S1 lesion on this lateral bias was tested using voxelwise symptom lesion

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mapping (VLBM) in a group of patients with large right-hemisphere strokes.

## Materials and Methods

### Study 1: spatial attention in a patient with a focal S1 lesion

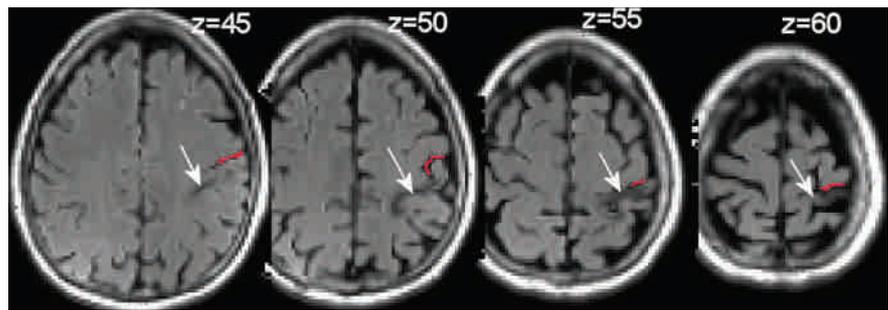
#### Participants

We investigated patient RW, a 69-year-old right-handed woman. Her vision was corrected to normal with glasses. RW had a focal intracerebral hemorrhage with a length of 3.6 cm centered on the right postcentral gyrus (Fig. 1). The lesion overlapped Brodmann area (BA) 3a, BA 2, and BA 1 as defined by the Juelich atlas (Geyer et al., 1996; Grekes et al., 2001; Eickhoff et al., 2005). On this atlas, it was possible to localize 94.6% of the lesion volume, 80% of it being in S1 (39.9% in area 2, 19.7% in area 3b, 15.9% in area 1, and 4.5% in area 3a). Less than 4% of the voxels were also found in area 7 (3.9%), area 4 posterior (3.2%), inferior parietal cortex (IPC) (2.9%), and area 4 anterior (2.8%). Her lesion overlapped with the projection of eye muscle proprioception in the sensorimotor cortex identified in healthy subjects (Balslev et al., 2011a). At the time of testing, ~3 years after stroke, RW had a proprioceptive deficit in the contralesional left eye (Balslev et al., 2012a). We found that, in normal conditions, the patient perceived her direction of gaze as accurately and precisely as the control group, presumably by relying on the efference copy of the oculomotor command. However, in special circumstances, when a mismatch between the efference copy of the oculomotor command and eye proprioception prompted the use of the erroneous eye proprioceptive information (i.e., a brief and gentle eye push applied to the closed eye), the patient underestimated her angle of gaze. Namely, after a brief push to the eyeball, she mislocated an LED at ~15° laterally as being in front of her nose (Balslev et al., 2012a).

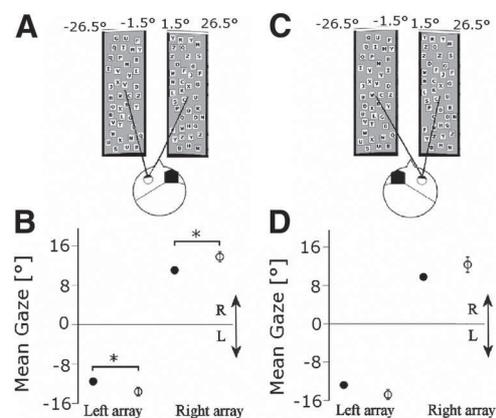
Neuropsychological assessments showed no neglect, no extinction, and no optic ataxia. The patient had normal, symmetric sensitivity to touch as assessed by two-point discrimination on the hands (Borchers et al., 2011) and face (Balslev et al., 2012a). As controls, we tested 11 healthy participants in Experiment A (10 women; mean age, 64.1 years; range, 59–74 years) and 14 healthy participants in Experiment B (11 women; mean age, 66.7 years; range, 60–74 years). The mean age in control groups was not significantly different from the patient's age [ $t$  test, single-case comparison (Crawford and Howell, 1998), both  $p > 0.35$ ]. All controls were right-handed and had normal or corrected-to-normal vision with glasses. All experiments were approved by the Ethics Committee at the University Clinic of Tübingen.

#### Procedure

**Experiment A.** This experiment investigated whether a lesion of the right postcentral gyrus affects the spatial distribution of fixations during visual search. The task was adapted from Karnath et al. (1998). The experiment was conducted in monocular vision. Although proprioceptive information from both eyes is relayed to each brain hemisphere (Balslev et al., 2011b), the input from the contralateral eye is functionally more important (Balslev et al., 2012a). The non-viewing eye was covered with a patch. The participants were instructed to look for a single, non-existent target (letter A) in a random field of letters while their gaze position was recorded. The letter arrays were placed laterally, to the left or right of the participants' midline. The head was fixed using a chin rest and cheek pads. They viewed a 25°-wide letter array (50° height) centered at 14° visual angle to the left or to the right of the orbit midline of the uncovered eye (Fig. 2A,C). The array showed randomly distributed black capital letters from B to Z (1° visual angle, 113 letters in the left array and 119 letters in the right array). Each letter was printed on a separate piece of white paper, attached to the display. Unbeknownst to the participants, the letter A was absent from the arrays, so the participants had to keep searching throughout the trial. Before each trial, the arrays were covered. At the beginning of the trial, the cover was removed and the participants were instructed to search one lateral array. Eye movements were re-



**Figure 1.** Focal lesion in the right postcentral gyrus in patient RW. The lesion (arrow) is shown in transversal slices through the patient's T1-weighted magnetic resonance image, after coregistration to the MNI152 template (International Consortium for Brain Mapping). The figure shows the central sulcus (red) and the vertical, z coordinate for each slice. The left side of the brain is shown to the left.

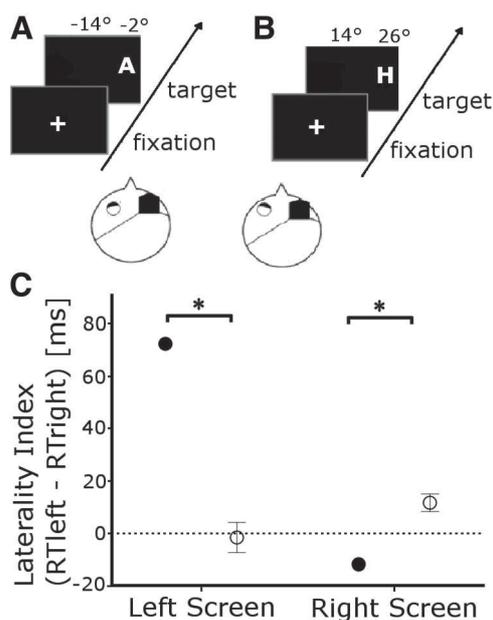


**Figure 2.** Mean gaze during visual search after a focal, right S1 lesion. Participants searched for a (nonexistent) target among random letters. The center of the letter array was at 14°, to the left or right of the orbit center. Mean gaze for the patient (filled circles) and a group of 11 healthy, age-matched, controls (open circles) are shown for the left (contralesional, **A, B**) and the right (ipsilesional, **C, D**) eye. Error bars represent the 95% confidence interval. Negative values on the y-axis describe leftward gaze, and positive values describe rightward gaze. Zero corresponds to the position of the midline of the orbit on a horizontal line. \* $p < 0.05$  for a single-case  $t$  test for a difference between patient RW and the control group (Crawford and Howell, 1998).

corded for 20 s, and then the array was again covered. Each participant completed four trials of 20 s duration, one for each lateral array and eye. The order of conditions was left eye–leftward array, left eye–rightward array, right eye–leftward array, and right eye–rightward array. To keep the participants motivated, in a practice trial before data registration, a letter A was attached at the center of the left array. If the participant did not find the target within 20 s, the experimenter identified its location by pointing to it.

Eye position was recorded with a head-mounted tracker (EYELINK II; SR Research) that sampled pupil location at 250 Hz. The tracker was calibrated for each lateral position of the array using a  $3 \times 3$  grid. Blinks and saccades were detected using the SR EyeLink algorithm. Saccades were defined by an amplitude of at least 0.5°, using an acceleration threshold of  $9500^\circ/\text{s}^2$  and a velocity threshold of  $30^\circ/\text{s}$ . After excluding blinks, we calculated mean eye position during visual search. To investigate whether changes in mean eye position were caused by changes in the fixation time or in the amplitude/frequency of the saccades, these parameters were calculated too and compared across conditions using the modified  $t$  test for the single-case comparison (Crawford and Howell, 1998).

**Experiment B.** This experiment investigated whether a lesion of the right postcentral gyrus causes a lateral asymmetry in visual sensitivity. The task, similar to that used previously (Odoj and Balslev, 2013), was performed in left (contralesional) monocular vision while the right eye was covered with a patch. The choice of the left eye was motivated by the



**Figure 3.** Increased visual sensitivity at locations nearer the midline after a right S1 lesion. In left eye vision, participants fixated at 14° to the left (**A**) or right (**B**) from the center of the left orbit. A target letter, A or H, was presented at 12°, to either the left or right of fixation with equal probability. The laterality index ( $RT_{\text{left}} - RT_{\text{right}}$ ) showed a significant interaction between group and gaze direction (**C**). Filled circles indicate the patient, and open circles indicate controls ( $n = 14$ , mean  $\pm$  SE). \* $p < 0.05$ , one-tailed single-case  $t$  test (Crawford and Howell, 1998).

results of Experiment A, as well as by the stronger impairment in proprioceptive inflow in the contralesional versus ipsilesional eye in RW (Balslev et al., 2012a). The head was fixed in a chin rest using cheek pads. A computer screen was positioned with its center at 14° to the left or to the right from the orbit midline of the left eye (Fig. 3A,B). At the start of the trial, a fixation cross (1°  $\times$  1°) was presented at the center of the screen for a randomized time interval between 1740 and 2540 ms. Then a target letter (A or H, 1°  $\times$  1°) appeared for 120 ms at 12° visual angle to either the left or right of fixation. The participant was instructed to fixate the cross throughout the trial and to respond as fast as possible whether he or she has seen an A or an H. A response was required for each trial, and if in doubt about the correct response, the participant was instructed to guess. To respond, the participant pressed one of two buttons on a response box using the right hand placed at the body midline. Participants used their index finger to respond A and middle finger for H. A new trial started immediately after a response. Each participant completed 288 trials, the first 144 with the screen on the left side and the last 144 trials with the screen on the right side. The different types of trials (target left/right, letter A/H) were equiprobable and intermixed in a pseudorandomized order, identical across all participants. Left–right asymmetries in visual sensitivity were indexed by a laterality index calculated as the difference between reaction times ( $RT_{\text{left}} - RT_{\text{right}}$ ). We compared this index across groups (patient vs controls) and screen conditions (left vs right). Because hand posture and motor response were the same across conditions, a group  $\times$  condition interaction in reaction time cannot be attributed to a sensorimotor deficit.

To verify fixation, the position of the left eye was recorded with a head-mounted tracker like in Experiment A. Mean gaze position was calculated for 200 ms before target onset. Only trials with a gaze deviation of  $<1^\circ$  from the fixation cross were included in the analysis (RW, 83.7%; control group,  $95.7 \pm 6.1\%$ , mean  $\pm$  SD).

## Study 2: VBLM in right-hemisphere stroke patients

### Participants

We reanalyzed patient data collected in two previous studies (Becker and Karnath, 2010; Karnath et al., 2011). From this data pool, we selected patients who suffered a first-ever stroke resulting in a right-hemisphere

lesion that was predominantly cortical (rather than subcortical) and that covered at least 50% of the perisylvian network identified previously to be associated with acute neglect (Karnath et al., 2011). To calculate how much of this region of interest was covered by each individual lesion, the statistical map resulting from the VBLM analysis conducted in the study of Karnath et al. (2011) was first converted into a binary map. Then the overlap percentage was calculated as the number of voxels within the region of interest that were lesioned in the individual patient, multiplied by 100 and divided by the total number of voxels of the region of interest.

A total of 15 patients (11 females; mean age, 64 years; range, 45–80 years) fulfilled the inclusion criteria. The selected patients had cortical ischemic lesions that covered on average 68.6% of the region of interest (range, 51.7–93.4%). Figure 4 shows a simple overlap of the brain lesions in the included patients. In accord with the inclusion criteria, all lesions were centered on the perisylvian region. However, because all lesions extended beyond this neglect-typical region, the figure shows additional areas that were lesioned in some but not all patients. Relevant for the hypothesis of this study, the area of partial overlap was distributed symmetrically around the right perisylvian region and included, among other areas, the right postcentral gyrus. This allowed us to investigate whether any of these areas of partial overlap had an effect on the neglect scores when lesioned compared with when intact.

### Imaging and behavioral data

The mean time from stroke onset to imaging for the selected patients was 1.1 d (range, 0–5 d). In the previous studies (Becker and Karnath, 2010; Karnath et al., 2011), lesions had been delineated using MRICroN software (Rorden et al., 2007; www.mricro.com). In those patients with spiral computed tomography scanning at admission ( $n = 9$ ), lesions had been drawn directly on the slices of a normalized T1-weighted template MRI scan from the Montreal Neurological Institute (MNI) with a 1  $\times$  1 mm in-plane resolution, distributed with the MRICroN toolset. In the patients who underwent MRI scanning at admission ( $n = 6$ ), the boundary of the lesion had been delineated directly on the image for every single transverse slice using MRICroN software. Both the MRI scan and the lesion shape then had been mapped into stereotaxic space using the normalization algorithm provided by SPM5 as well as cost–function masking when calculating transformation parameters (Brett et al., 2001).

The severity of spatial neglect was indexed by the center of cancellation (CoC) measure (Rorden and Karnath, 2010) obtained from the letter cancellation task (Weintraub and Mesulam, 1985), the Bells test (Gauthier et al., 1989), and/or the Albert's test (Albert, 1973). The tests were performed as soon as the patients were able to participate, on average 4.9 d after stroke (range, 0–19 d). When more than one test result was available (80% of cases), the CoC measures were averaged across tests. The mean  $\pm$  SD CoC score for all patients was  $0.64 \pm 0.34$ . Twelve of these 15 patients had spatial neglect, defined as a CoC  $> 0.083$  (Rorden and Karnath, 2010).

### Data analysis

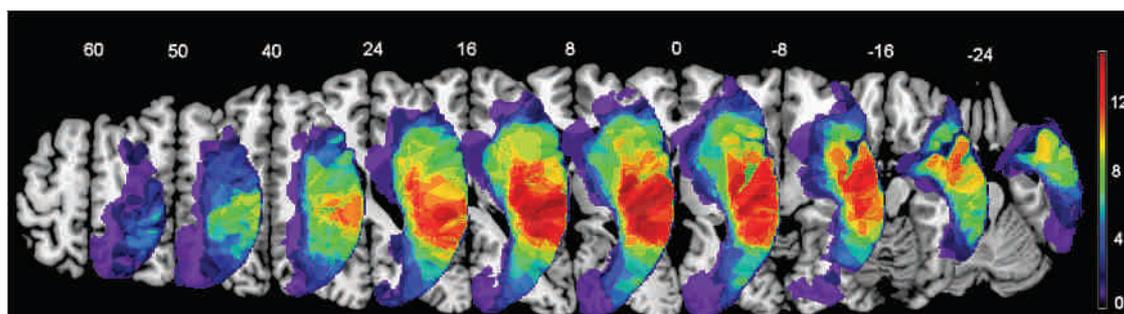
The imaging and behavioral data were entered into a VBLM analysis. The analysis is implemented in MRICroN using  $t$  test statistics and the continuous CoC score as the dependent variable. This analysis identified voxels whose lesion is correlated with a less severe neglect, i.e., with lower CoC scores, as well as with a more severe neglect, i.e., higher CoC scores. Only voxels in which at least 20% of patients ( $n = 3$ ) were assigned to each statistical group were included. This was done to avoid a possible influence from just one or two data outliers. The threshold for statistical analysis was set at 0.05 and corrected for multiple comparisons using false discovery rate (FDR).

## Results

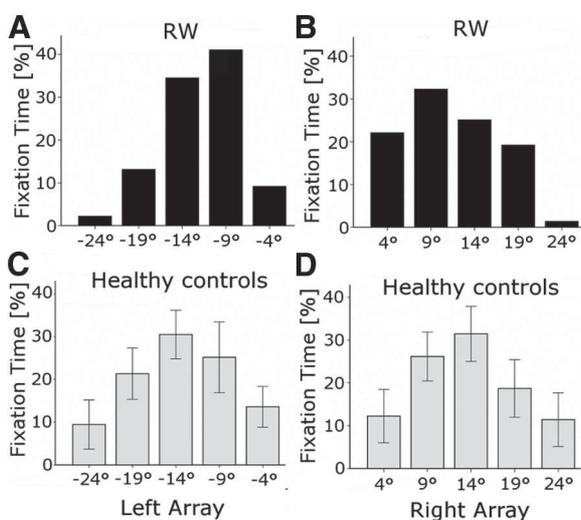
### Study 1: spatial attention in a patient with a focal S1 lesion

*RW fixates longer at locations nearer the midline during visual search*

To investigate whether an S1 lesion causes a bias in spatial attention, we recorded gaze direction while the subjects searched in lateral letter arrays. We hypothesized a lateral shift in the spatial



**Figure 4.** Simple overlap of the individual lesions for the 15 patients included in Study 2. For each voxel, the number of patients with a lesion at that location is color coded. The color map is superposed on a single-subject T1 template coregistered with the MNI152 template. Conventions as in Figure 1.



**Figure 5.** Distribution of the fixation time during visual search after an S1 lesion. In left (contralateral) eye vision, the patient fixated longer in the inner area of the left (**A**) and right (**B**) arrays, whereas the distribution of the fixation time in the healthy controls (**C, D**) was symmetrical relative to the center of the arrays. The figure shows the percentage of the fixation time spent in each 5° sector of the arrays along the horizontal axis. For healthy controls ( $n = 11$ ), the bars show mean  $\pm$  1 SD. The position of the left orbit midline is at 0°.

distribution of fixation time. In accord with this hypothesis, mean eye position during visual search in RW was  $\sim 2^\circ$  nearer the midline compared with that of the healthy, age-matched controls. Mean eye position in RW for the left eye was  $-11.5^\circ$  in the left array and  $11.1^\circ$  in the right array, whereas in the control group these values were  $-13.7 \pm 0.9^\circ$  and  $13.8 \pm 1.08^\circ$ , respectively (Fig. 2B). Mean eye position in RW for the right eye was  $-12.7^\circ$  in the left array and  $9.8^\circ$  in the right array. In the control group, the mean eye position was  $-14.7 \pm 1.0^\circ$  and  $12.3 \pm 1.6^\circ$  (Fig. 2D). The modified  $t$  test for the single-case comparison (Crawford and Howell, 1998) showed a statistically significant difference for the contralateral left eye ( $t = 2.28$ ,  $p = 0.045$  for left array and  $t = -2.42$ ,  $p = 0.035$  for right array). For the ipsilesional right eye, we found a numerical difference in the same direction, which was not statistically significant ( $t = 1.86$ ,  $p = 0.09$  for left array and  $t = -1.55$ ,  $p = 0.15$  for right array).

The shift in mean eye position in RW's left eye was caused by a shift in the spatial distribution of the fixation time (Fig. 5). The patient fixated 55.38% longer in the inner versus outer half of the left array (control group,  $5.27 \pm 19.00\%$  longer in the inner half) and 37.91% longer in the inner versus outer half of the right array (control group,  $1.43 \pm 14.20\%$  longer in the inner half). The modified  $t$  test for the single-case comparison (Crawford and

Howell, 1998) showed a statistically significant difference between these values ( $t = -2.52$ ,  $p = 0.030$  for left array and  $t = 2.46$ ,  $p = 0.034$  for right array).

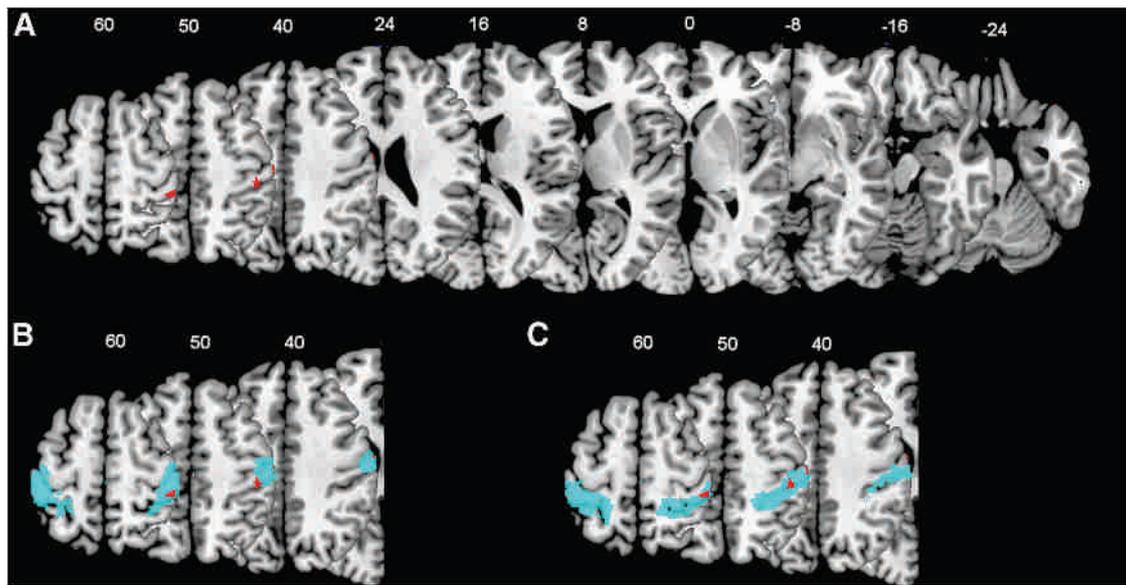
Thus, the results of Experiment A show a bias in visual exploration toward the midline after an S1 lesion. This contrasts with the bias in opposite direction, away from midline, found previously after inhibitory rTMS in the same area (Odoj and Balslev, 2013). A notable difference between the two studies is that an acute decrease of the excitability of the eye proprioceptive area with rTMS causes an error in perceived gaze direction toward the midline (Balslev and Miall, 2008; Odoj and Balslev, 2013), whereas a chronic lesion in this area, although it interferes with the processing of the eye proprioceptive input, does not affect the gaze position estimate (Balslev et al., 2012a). Therefore, the apparent contradiction between the two results can be resolved by assuming that the shift in exploratory eye movements away from midline after rTMS in the study by Odoj and Balslev (2013) may have reflected a misperception of the direction of gaze, i.e., the participants may have felt their gaze to be less eccentric than it actually was and therefore searched at more peripheral locations in the array. After a chronic S1 lesion in patient RW, the gaze angle is correctly perceived (Balslev et al., 2012a). This may be the reason why, here, the same spatial bias was observed in both visual sensitivity (Experiment B) and visual exploration (Experiment A).

#### *RW's bias toward the midline in looking time cannot be explained by a lower-level oculomotor deficit*

One could object that the shift in mean eye position and fixation time toward the midline in RW reflects an inability to move the eyes toward peripheral locations or altered saccade metrics. We think that these explanations are unlikely for the following reasons.

First, Experiment A did not find a difference between RW and the control group in the range of eye movements. When viewing the array with the left eye, the patient moved her gaze between  $[-22.0^\circ$  to  $-2.7^\circ]$  for the left and  $[2.0^\circ$  to  $22.4^\circ]$  for the right array. For the left array, controls moved their gaze between  $-24.7 \pm 1.7^\circ$  and  $-2.2 \pm 0.8^\circ$  (mean  $\pm$  SD). For the right array, the movement interval in healthy controls was between  $3.1 \pm 1.0^\circ$  and  $24.5 \pm 2.3^\circ$ . None of these values were significantly different from the values in the patient (modified  $t$  tests for single-case comparison, all  $p > 0.16$ ).

Second, we found no significant difference between RW and the control group in the number of fixations in the left/right half of the letter arrays. All modified  $t$  tests for the single-case comparison showed  $p > 0.24$ . Likewise, the analysis of saccade frequency or amplitude showed no significant difference between RW and the control group for any of the four combinations of



**Figure 6.** Brain areas in which an additional lesion was associated with milder neglect, given a primary lesion in the perisylvian network region. The statistical map (red) is thresholded at  $p < 0.05$ , FDR corrected ( $z$  score  $> 2.16$ ) and overlaid on a single-subject T1 template coregistered with the MNI152 template (**A**). The probabilistic maps from the Juelich atlas (Geyer et al., 2000; Grefkes et al., 2001; Eickhoff et al., 2005) for BA 1 (**B**) and BA 2 (**C**) thresholded at a voxel probability for the BA = 25% are shown in blue. Conventions as in Figure 1.

saccade direction (leftward or rightward) and array (left or right). All modified  $t$  tests for the single-case comparison showed a  $p > 0.48$  for amplitude and a  $p > 0.07$  for frequency. There was a numerical tendency for fewer leftward saccades while searching the left array in the patient compared with the controls ( $p = 0.07$ ). For the other combinations of saccade direction, array, and eye, all  $p$  values were 0.21.

#### *RW shows a gradient in visual sensitivity that favors locations nearer midline*

The argument for a role of S1 in visuospatial attention and against a purely ocular sensorimotor explanation for the asymmetry in fixation time in Experiment A is based on a null result. To address this shortcoming, Experiment B investigated spatial attention using a task in which the sensorimotor response was the same in all conditions. Like Experiment A, Experiment B showed a spatial bias toward midline in RW. RW needed longer time to discriminate targets located further versus nearer from midline, and this difference was significantly larger in the patient than in the control group (Fig. 3C). In leftward gaze, the laterality index for reaction time ( $RT_{\text{left}} - RT_{\text{right}}$ ) was  $\sim 74$  ms higher in RW (72 ms) than in controls [ $-2 \pm 22$  ms, mean  $\pm$  SD; one-tailed single-case  $t$  test Crawford and Howell, 1998),  $t = 3.32$ ,  $p = 0.003$ ]. In rightward gaze, this index was  $\sim 24$  ms lower in RW ( $-12$  ms) than in controls ( $12 \pm 13$  ms; one-tailed single-case  $t$  test,  $t = 1.78$ ,  $p = 0.049$ ). One-tailed  $t$  tests were used because of the a priori hypothesis that visual sensitivity would increase nearer the midline after an S1 lesion (Odoj and Balslev, 2013). A repeated-measures ANOVA with factors direction of gaze (leftward or rightward) and group (RW or controls) implemented as an unstandardized difference test (Crawford et al., 1998; Crawford and Garthwaite, 2005) showed a significant interaction for the laterality index ( $p = 0.001$ , correlation between the difference in reaction times for the leftward and rightward gaze condition in the control group,  $r = 0.2$ ). Like in previous studies (Balslev et al., 2011b, their Fig. 3; Odoj and Balslev, 2013, their Fig. 2), an incidental observation was a rightward bias in healthy controls when the

screen was placed to the right of midline (single-sample  $t$  test,  $t = 3.47$ ,  $p = 0.004$ ).

Discrimination accuracy for the control group over all conditions approached ceiling (screen left,  $97.3 \pm 2.1\%$ ; screen right,  $96.9 \pm 2.8\%$ ) and was not significantly different compared with RW (95.3% screen left and 97.9% screen right, single-case comparisons, all  $p > 0.3$ ).

In summary, Study 1 showed that an S1 lesion is associated with longer fixations at locations nearer midline during visual search (Experiment A) and an advantage for visual discrimination at these locations (Experiment B). These results suggest that an S1 lesion causes a bias in spatial attention that favors locations nearer the midline.

#### **Study 2: VBLM in right-hemisphere stroke patients**

##### *Coinjury of S1 together with the neglect-typical perisylvian lesion is associated with a milder neglect*

Patients with a right perisylvian stroke show contralesional neglect, namely a rightward bias in spatial attention (Karnath and Rorden, 2012). Notably, during visual search, neglect patients prefer to fixate away from the midline, in their right ipsilesional hemispace (Hornak, 1992; Karnath, 1994; Karnath et al., 1998). Because an isolated S1 lesion leads to a bias in spatial attention toward the midline, we hypothesized that, when S1 and the perisylvian network are injured together, the sum of the two effects may lead to a milder left-sided neglect. Study 2 investigated whether the coinjury of the postcentral gyrus in patients with a lesion of the perisylvian network reduces the rightward bias. This study was conducted in patients whose right hemisphere stroke overlapped at least 50% of the neglect-typical perisylvian region. Using VLBM, we searched for brain areas associated with a milder left neglect when lesioned rather than when intact. In accord with the hypothesis, an S1 lesion correlated with a lower neglect score. The area in the postcentral gyrus was the only cluster of voxels above the threshold (Fig. 6A; threshold  $p < 0.05$ , FDR corrected,  $z$  score  $> 2.16$ ). Sixty-three percent of voxels were assigned to BA 1 (Fig. 6B) and 25% to BA 2 (Fig. 6C) according to

the Juelich atlas (Geyer et al., 2000; Grefkes et al., 2001; Eickhoff et al., 2005). Approximately 4% of the voxels were assigned to each of the areas 3b, 6, and IPC.

When we increased the sensitivity in a second VBLM analysis by excluding those voxels representing the perisylvian network region (and thus reducing the number of multiple comparisons), we again found only one cluster of significant voxels in the somatosensory cortex (threshold  $p < 0.05$ , FDR corrected,  $z$  score  $> 1.65$ ). Sixty-two percent of these voxels were assigned to BA 1 and 32% to BA 2 according to the Juelich atlas.

Please note that the patients in the current analysis had a right hemisphere, predominantly cortical, lesion so the modulatory role of other brain areas known to alleviate left neglect when colesioned—such as the left frontal eye field (Vuilleumier et al., 1996), the left posterior parietal cortex (Brighina et al., 2003; Nyffeler et al., 2009), or superior colliculus (Sprague, 1966; Weddell, 2004)—could not be examined here.

The opposite comparison, which looked for brain areas associated with a more severe neglect when injured versus when intact, yielded no statistically significant voxels outside the perisylvian network region used to select the patients.

#### *Neither lesion size nor the demographics can explain the lower CoC in the patients with S1 coinjury*

Eight of the patients included in Study 2 had a lesion that fully or partially overlapped the somatosensory area identified by the VBLM analysis (Group 1), whereas in the remaining seven, the lesion did not cover this area (Group 2). As expected, Group 1 had a significantly milder neglect than Group 2 (mean  $\pm$  SD CoC,  $0.48 \pm 0.37$  vs  $0.85 \pm 0.09$ , independent-samples  $t$  test,  $t = 2.6$ ,  $p = 0.027$ ). Although Group 1 had a lower neglect score, there was a numerical trend for the lesions in this group to overlap a larger percentage of the critical neglect area ( $75 \pm 13\%$  in Group 1 vs  $62 \pm 12\%$  in Group 2,  $t = 1.94$ ,  $p = 0.073$ ). The groups did not differ significantly in any of the other variables we measured, such as lesion size ( $13.2 \pm 4.1$  vs  $10.6 \pm 3.6$  cm<sup>3</sup>,  $t = 1.29$ ,  $p > 0.21$ ), age ( $67 \pm 16$  vs  $62 \pm 15$  years,  $t = 0.65$ ,  $p > 0.5$ ), or time between the lesion and the neuropsychological testing ( $7 \pm 7$  vs  $3 \pm 1.4$  d,  $t = 1.25$ ,  $p > 0.24$ ).

Study 2 thus singled out the somatosensory cortex as the area associated with a milder left neglect when lesioned compared with when intact. These voxels were selected from a larger area in the cortex of the right hemisphere, located symmetrically around the neglect-typical lesion.

## Discussion

An isolated S1 lesion caused a gradient in visual exploration as well as in visual sensitivity that favored locations nearer the midline. RW's bias in looking time despite normal oculomotor ability as well as the spatial asymmetry in her ability to discriminate retinally identical targets suggest that S1 plays a role in the allocation of attention in the body-centered space.

These results cannot be explained by an asymmetry in the motor response. First, Experiment A showed no significant difference between RW and controls in the range of eye movements or saccade metrics. RW's normal oculomotor range despite a lesion of the eye proprioceptive area is not surprising. The amplitude of visually guided saccades in both monkeys (Guthrie et al., 1983) and humans (Allin et al., 1996) was unimpaired when the eye proprioceptive input was removed or altered. A second and stronger argument than this null result is RW's spatial asymmetry in visual discrimination in Experiment B. In this experiment, participants fixated the gaze and responded using the same movements in all conditions. Therefore, a difference in reac-

tion time between conditions cannot easily be attributed to an asymmetry in motor performance.

The current results do not reflect the patient's error in locating visual targets. Despite an erroneous proprioceptive signal from the left eye, this patient can, under normal circumstances, locate visual stimuli relative to the body as accurately and as precisely as healthy controls (Balslev et al., 2012a). This result is in line with the suggestion that, for locating visual objects relative to the body, the brain relies on the efference copy of the motor command rather than on eye proprioception (Lewis et al., 1998). Proprioceptive information is incorporated into the estimate of gaze only in special circumstances, when a mismatch with the efference copy is detected. Examples of such conditions are passive eye movement (Gauthier et al., 1990; Balslev et al., 2012a) or rTMS over the anterior parietal cortex (Balslev and Miall, 2008) but not a chronic S1 lesion (Balslev et al., 2012a).

A shift in visual exploration or visual sensitivity away from the periphery and toward the midline is not a general consequence of a right-hemispheric brain lesion. After such lesions, patients with or without spatial neglect have been tested on tasks similar to those in Experiment A (Karnath et al., 1998) and Experiment B (Smania et al., 1998). Neither of these studies found a bias toward the midline in spatial attention like that reported here. Instead, they observed a bias in the opposite direction, i.e., away from the midline and toward the ipsilesional periphery in neglect patients and the absence of a gradient in brain-damaged patients without neglect. This differs from the current findings and can thus rule out that a right-hemisphere lesion alone, regardless of its location, leads to a bias toward the midline in spatial attention.

Although the lesion in RW was limited to the postcentral gyrus, it is possible that a functional impairment that could not be detected in structural scans (i.e., a decrease in perfusion) could have reached farther into the surrounding areas. However, we are not aware of another brain area that, when lesioned, biases attention toward the midline. A function impairment in the posterior parietal or superior/middle temporal lobe—after a lesion (Karnath et al., 1996) or after an rTMS-induced “virtual lesion” (Nyffeler et al., 2008)—can bias visual exploration toward the contralesional space. This differs from the current findings. Likewise, we cannot exclude the possibility of a lesion of the connecting fibers between the intraparietal sulcus and the frontal eye field in RW. However, because these areas code saccade direction/salient locations in the contralateral visual hemifield or contralateral body hemisphere (Silver et al., 2005; Silver and Kastner, 2009; Szczepanski et al., 2010), it is unlikely that a lesion of these areas or their projection fibers could have caused the midline-periphery gradient found here. Instead, this midline-periphery gradient fits well with the organization of the primary eye proprioceptive area. In monkeys, area 3a neurons increase their firing with ocular eccentricity for all directions of gaze (Wang et al., 2007). Assuming that the eye proprioceptive area in humans is organized in the same way, it is plausible that its lesion causes a gradient in attention from midline to periphery, in both ipsilesional and contralesional hemisphere.

A lateral bias in visual exploration is a characteristic of patients with spatial neglect. These patients have a lesion centered on the sylvian sulcus, usually on the right side, which causes a shift in fixation time away from the midline and toward the ipsilesional hemisphere (Hornak, 1992; Karnath, 1994; Karnath et al., 1998). The results of Study 2 showed that the extension of the neglect typical perisylvian lesion into S1 reduces this lateral bias and thus leads to a milder neglect. This VBLM analysis included cortical voxels distributed symmetrically around the right sylvian sulcus

to identify those whose lesion correlated with a reduced neglect severity. The only brain area identified by this analysis was located in S1. The subgroups of patients with and without an S1 coinjury did not differ significantly in lesion size, in the overlap between the lesion with the neglect-typical perisylvian area, in age, or in the time elapsed between stroke and neuropsychological testing. Thus, these variables cannot explain the milder neglect score in the subgroup of patients with S1 coinjury. The finding that an additional brain lesion can be an advantage for performance in neglect patients is counterintuitive. However, the shift in spatial selection toward midline after an isolated S1 lesion in Study 1 provides an explanation for the reduced lateral bias when the neglect-typical perisylvian lesion extends into this area.

We can think of two limitations in interpreting the current study. First, the current setup does not allow to tell whether this bias toward the midline after an S1 lesion occurred relative to a reference frame centered on the orbit, head, or trunk. This question can be addressed by further studies that dissociate head and trunk midline and present search arrays that are placed symmetrical relative to one of these body anchors.

Second, this study cannot answer where precisely S1 exerts its modulatory effect in the visual processing stream toward a motor response. Functional neuroimaging in patients with an S1 lesion would be needed to answer this question. In a previous study in which rTMS was applied to S1, we observed a modulation of the functional MRI activity in the cuneus (Balslev et al., 2012c). This variation in neural activity mirrors the center-to-periphery gradient in visual sensitivity observed here. These previous neuroimaging findings suggest that S1 could exert its modulatory activity on visual processing already at visual cortex level.

Spatial attention can be defined as the selection of locations for perception and/or for action (Bisley and Goldberg, 2010; Petersen and Posner, 2012). Within this framework, Studies 1 and 2 suggest a role of S1 in spatial attention. Given the neuroanatomical analogies between the oculomotor and spatial attention system (Corbetta, 1998), we hypothesize a coupling between the eye proprioceptive signal in S1 and spatial attention. One possibility is that the function of S1 in spatial attention and in signaling the direction of gaze relies on independent neural populations that share the same principle of organization. For instance, this is the case in the frontal eye field, in which separate neural populations code the direction of a saccade and an attention shift (Juan et al., 2004; Thompson et al., 2005). A second possibility is that the locus of attention may be coded relative to the body by using a gaze-direction signal that has a proprioceptive component. We observed previously that direct manipulation of the extraocular muscles causes spatial gradients in visual attention (Balslev et al., 2012b). A role of eye proprioception in coding the locus of attention would be compatible with the delay in updating the locus of attention after an eye movement of ~100–200 ms found in a previous study (Golomb et al., 2008). It would also be consistent with the latency of 150 ms until the gain field neurons in the lateral intraparietal area, which use eye position to implement non-retinotopic representations (Andersen et al., 1985), update their firing to reflect the new gaze direction after a saccade (Xu et al., 2012). These delays are in the same order of magnitude as the time needed by the eye proprioceptive signal to reach the cerebral cortex, ~60 ms (Xu et al., 2011).

## Conclusion

A lesion in the right S1, when it occurs in isolation, biases visual exploration and visual sensitivity toward the midline. When an

S1 lesion occurs as a part of a large perisylvian stroke, it is associated with a reduced bias toward the ipsilesional space and thus with a milder spatial neglect. These results argue for a novel role of the somatosensory cortex in visuospatial attention. We hypothesize that the proprioceptive gaze signal in S1, although playing only a minor role in locating visual objects relative to the body, affects the allocation of attention in the visual space.

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# Role of Oculoproprioception in Coding the Locus of Attention

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## Abstract

■ The most common neural representations for spatial attention encode locations retinotopically, relative to center of gaze. To keep track of visual objects across saccades or to orient toward sounds, retinotopic representations must be combined with information about the rotation of one's own eyes in the orbits. Although gaze input is critical for a correct allocation of attention, the source of this input has so far remained unidentified. Two main signals are available: corollary discharge (copy of oculomotor command) and oculoproprioception (feedback from extraocular muscles). Here we asked whether the oculoproprioceptive signal relayed from the somatosensory cortex contributes to coding the locus of attention. We used continuous theta burst stimulation (cTBS) over a human oculoproprioceptive area in the postcentral

gyrus (S<sub>1EYE</sub>). S<sub>1EYE</sub>-cTBS reduces proprioceptive processing, causing ~1° underestimation of gaze angle. Participants discriminated visual targets whose location was cued in a non-visual modality. Throughout the visual space, S<sub>1EYE</sub>-cTBS shifted the locus of attention away from the cue by ~1°, in the same direction and by the same magnitude as the oculoproprioceptive bias. This systematic shift cannot be attributed to visual mislocalization. Accuracy of open-loop pointing to the same visual targets, a function thought to rely mainly on the corollary discharge, was unchanged. We argue that oculoproprioception is selective for attention maps. By identifying a potential substrate for the coupling between eye and attention, this study contributes to the theoretical models for spatial attention. ■

## INTRODUCTION

Attention allows organisms to focus on relevant stimuli. In monkeys, neurons that respond to attended stimuli have a retinotopic receptive field, which reference location relative to the direction of gaze (Gottlieb, Kusunoki, & Goldberg, 1998; Andersen & Mountcastle, 1983). A retinotopic code for attended stimuli has also been observed in humans. Indeed, although visual perception is normally facilitated at the location indicated by an attention cue, just after an eye movement, attention can be transiently allocated away from the cue, at its previous retinotopic coordinates (Talsma, White, Mathôt, Munoz, & Theeuwes, 2013; Golomb, Nguyen-Phuc, Mazer, McCarthy, & Chun, 2010; Mathôt & Theeuwes, 2010; Golomb, Chun, & Mazer, 2008).

Retinotopic representations alone cannot support cross-modal interactions in spatial attention between visual and nonvisual modalities or maintain a stable focus of attention across eye movements. One solution to this problem could be to create coregistered representations in multiple reference frames (Pouget, Deneve, & Duhamel, 2002; Andersen, Snyder, Bradley, & Xing, 1997). Another solution could be to update the retinotopic representation for each eye movement (Duhamel, Colby, & Goldberg,

1992). Importantly, both solutions require information about the rotation of the eyes in the orbits. Despite the importance of the gaze information in the brain's representations for spatial attention, the sources of this gaze input to the attention maps remain unknown. The main sources of eye position are the feedback from the extraocular muscles or oculoproprioception (Sherrington, 1918) and an internal model that predicts future eye rotation based on the copy of the oculomotor command or corollary discharge (von Helmholtz, 1925).

Does oculoproprioception play a role in coding the locus of attention? On the one hand, some studies fail to find a decrease in accuracy or precision of visual localization in conditions when oculoproprioception is reduced or abnormal (Balslev, Himmelbach, Karnath, Borchers, & Odoj, 2012; Lewis, Gaymard, & Tamargo, 1998; Guthrie, Porter, & Sparks, 1983). Such findings support the suggestion that oculoproprioception does not normally contribute to the estimate of eye rotation but rather calibrates the oculomotor command in the long term (Wurtz, 2008; Steinbach, 1986).

On the other hand, some behavioral studies (Talsma et al., 2013; Golomb et al., 2008, 2010; Mathôt & Theeuwes, 2010) show delays in updating the retinotopic coordinates where attention is deployed after a saccade. These delays are compatible with the delay in the ascending fibers (Xu, Wang, Peck, & Goldberg, 2011; Wang, Zhang, Cohen, &

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Goldberg, 2007) and therefore leave open the possibility that oculoproprioception may contribute. Furthermore, we have observed alterations in visual sensitivity in conditions that distort the oculoproprioceptive signal. The oculoproprioceptive signal was distorted in the ocular periphery, using passive eye rotation (Balslev, Newman, & Knox, 2012), or centrally, in the somatosensory cortex, after repetitive TMS (Odoj & Balslev, 2013; Balslev, Gowen, & Miall, 2011) or after a focal lesion (Balslev, Odoj, & Karnath, 2013). These previous studies suggest a link between the oculoproprioceptive signal in the somatosensory cortex and spatial attention; however, the nature of this link is still unclear. One possibility is that the *attention* map incorporates oculoproprioception, so that a distortion of this signal causes a systematic shift in the locus of attention relative to a cue. Another possibility is that the visual map incorporates oculoproprioception, so that a distortion of this signal causes a systematic error in locating visual targets relative to the body. Visual stimuli presented nearer the hand (Reed, Grubb, & Steele, 2006), the head midline (Durand, Camors, Trotter, & Celebrini, 2012; Durand, Trotter, & Celebrini, 2010), or the trunk midline (Grubb, Reed, Bate, Garza, & Roberts, 2008) have a privileged access to neural processing resources compared with visual stimuli presented elsewhere. A mislocalization of the visual stimuli relative to these landmarks could, in our previous studies, have changed their neural processing priority.

Here, we investigated whether oculoproprioception is incorporated in attention maps.

Oculoproprioception was manipulated using continuous theta burst stimulation (cTBS), a form of inhibitory TMS, over an oculoproprioceptive area in the human postcentral gyrus (S1<sub>EYE</sub>). Inhibitory repetitive TMS over S1<sub>EYE</sub> interferes with the ability to correct for passive eye movement during a visual localization task (Balslev & Miall, 2008) and results in an underestimation of the rotation of the eye in the orbit by  $\sim 1^\circ$  (Odoj & Balslev, 2013). We used S1<sub>EYE</sub>-cTBS over the left postcentral gyrus to alter the oculoproprioceptive signal. Participants discriminated visual targets whose location was cued by the position of their unseen left index finger or pointed to these targets using the same finger. Both tasks depend critically on eye position information to match the location of the visual target with the location of the finger that acted either as an attention cue or as an effector.

We report a systematic error in the locus of attention and no pointing error after S1<sub>EYE</sub>-cTBS. We argue therefore that oculoproprioception is the eye position signal that is selective for the attention map.

## METHODS

### Overview of the Experiments

Experiment 1 examined the allocation of attention using a cross-modal task. Participants discriminated a visual target. The location of this target was cued by the location

of the unseen left index finger. The locus of attention was defined as the location in the visual space where the cue had the largest effect on the RT for target discrimination. If oculoproprioception is incorporated into the attention maps, one would predict a systematic error in the locus of attention relative to the location of the cue after S1<sub>EYE</sub>-cTBS.

Experiment 2 examined visuospatial localization using an open-loop pointing task. Participants used their unseen left index finger to reach to visual targets in the absence of visual feedback. If oculoproprioception is incorporated into visual maps, one would predict a systematic error in open-loop pointing after S1<sub>EYE</sub>-cTBS.

Experiment 3 examined participants' ability to locate their unseen left index finger using an open-loop pointing task. This experiment controlled for an effect of S1<sub>EYE</sub>-cTBS on the ability to locate the nonvisual cue in Experiment 1.

All experiments were conducted with the participants fixating rightward (Experiments 1A–3A) and leftward (Experiments 1B–3B). The reason for repeating the experiment for different directions of gaze was the following. The effect of S1<sub>EYE</sub>-cTBS on visual localization is gaze dependent, that is, a shift in perceived eye rotation toward left in rightward gaze and toward right in leftward gaze (Odoj & Balslev, 2013), reflecting the underestimation of the rotation of the eyes in the orbits. We predicted therefore that the change in the direction of gaze would reverse the effect. In this way, one can separate a specific, gaze-dependent effect, from a general influence of anterior parietal cortex on attention (Experiment 1) or reaching (Experiments 2–3).

### Participants

We tested 10 participants (five women) in each of three different experiments (Experiments 1–3). All were right-handed with normal or corrected-to-normal vision. For Experiments 1A–3A, participants had an age range from 22 to 32 years (median: 28.5 years). For Experiments 1B–3B, participants had an age range from 27 to 32 years (median: 29 years). Five participants took part in all experiments (A and B). All participants gave their informed consent. The study was approved by the local ethics committee at the University of Tübingen.

### Experiment 1. Attention Map

This experiment investigated whether oculoproprioception is included in the eye position estimate necessary for orienting attention in the visual space in response to a nonvisual cue.

Participants discriminated a target (letter “A” or “H”, size  $1^\circ$  visual angle) whose most probable location was indicated by a somatosensory cue, the location of the participant's left index finger hidden from view. We assumed that cTBS of the ipsilateral, left somatosensory cortex will have

only a small effect, if any on perceiving finger location. This assumption was explicitly tested in Experiment 2. The experimenter placed the participant's index finger just below the horizontal line where targets were presented. To assess the benefit of the cue, we calculated the difference in RT for visual discrimination in the presence versus the absence of the cue. The locus of attention was the location with the largest benefit of the cue. "Cueing error" was defined as the distance between the locus of attention and the actual location of the cue. If eye proprioception contributes to coding the locus of attention, S1<sub>EYE</sub>-cTBS should increase cueing error by causing a shift in the locus of attention away from the cue and toward the center of the orbit, in the same direction as the shift in perceived eye position.

### Setup

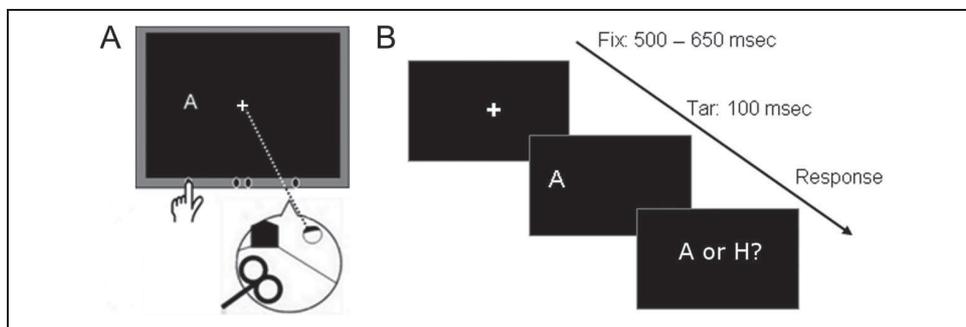
Participants sat with their head fixed in a chin rest and cheek pads. A cathode ray tube (CRT) display was placed at 45 cm in front of them (Figure 1A). The CRT was centered at +19° (Experiment 1A) or at -19° (Experiment 1B, Figure 1) from center of the right orbit. Participants performed the task in right eye vision, with the left eye patched. The experiment was conducted in monocular vision for the following reason. In the macaque, the primary oculoproprioceptive area 3a receives proprioceptive information from the contralateral eye only (Wang et al., 2007). In humans, although proprioceptive information from both eyes is relayed to each brain hemisphere (Balslev, Albert, & Miall, 2011), the input from the contralateral eye is functionally more important (Balslev, Himmelbach, et al., 2012). Therefore, we assumed that after cTBS of one hemisphere (left), the effects would be strongest and easier to measure for the contralateral eye (right). As a somatosensory cue, we used the position of the participants' left index finger, ipsilateral to the hemisphere where TMS was applied. A transparent (Plexiglas) sheet was mounted 5 cm in front of the CRT

screen. Participants had their left index finger on a support (a wooden ledge) attached to the Plexiglas immediately under the location where the targets would appear. The finger was placed at one of four possible cue positions, 8°, 18°, 20°, or 30° to the right (Experiment 1A, rightward gaze) or left (Experiment 1B, leftward gaze) from orbit midline of the right eye and covered with black cloth by the experimenter. The experiment took place in total darkness. The participants had no visual information about finger location (somatosensory cue) to prompt the use of gaze information to locate the visual targets relative to the cue.

At the beginning of the trial, participants fixated on a central cross (white, 1° × 1°) presented on black background (Figure 1B). Fixation was verified with a head-mounted eye tracker (EyeLink II, SR Research Ltd., Ottawa, Canada). After 500–650 msec (randomized), the fixation cross disappeared. At 100 msec later, a target letter ("A" or "H," 1° visual angle) appeared for 100 msec. The target appeared at one of seven possible locations, at -3°, -2°, -1°, 0°, 1°, 2°, and 3° from the somatosensory cue. Participants were told that the target letter is most likely to appear at the location indicated by the cue. The target letter was however presented with equal probability (eight times) at each of the seven possible target locations. Additionally, three trials showed target letters at random locations outside this range so that the participants could not predict the location of the nonvisual cue from the spatial distribution of the visual targets. The participants were instructed to name the target letter as fast and accurately as possible. Voice RT was recorded.

Trials with the same cue location were grouped in blocks. Each block consisted of 59 trials (8 trials for each of the 7 target positions + 3 random positions). Trial order was pseudorandomized. At the end of each block, participants were instructed to close their eyes. Then the experimenter moved the participants' index finger at the next cue location and started a new block. The participants completed four cued blocks (cue at +8°, +18°, -8°, -18°, -20°, or -30° (Experiment 1B) from orbit midline (here, Experiment 1B: fixation at -19°, cue at -30° from orbit midline)).

**Figure 1.** Setup and task for the cross-modal attention experiment. (A) In right eye vision, participants fixated at +19° (Experiment 1A, rightward gaze) or -19° (Experiment 1B, leftward gaze) from the center of the right orbit. A somatosensory cue (the participants' left index finger, hidden from view) was positioned at one of four possible locations: +8°, +18°, +20°, or +30° (Experiment 1A) or -8°, -18°, -20°, or -30° (Experiment 1B) from orbit midline (here, Experiment 1B: fixation at -19°, cue at -30° from orbit midline). (B) A target letter, "A" or "H," was presented for 100 msec at one of seven possible locations, at -3°, -2°, -1°, 0°, +1°, +2°, and +3° horizontally from the cue. Participants named the letter as fast and correct as possible. Voice RT and accuracy were recorded. The solid line shows eye position at fixation. The dotted line shows perceived eye position after S1<sub>EYE</sub>-cTBS according to Odoj and Balslev (2013). We predicted a shift of the locus of attention congruent to the shift in perceived gaze toward the center of the orbit for all cue locations.



+20° or +30° from orbit midline in Experiment 1A and -8°, -18°, -20° or -30° in Experiment 1B). The order of the blocks was pseudorandomized.

To assess the baseline distribution of attention as well as visual accuracy, participants performed the same visual discrimination task in the absence of a cue. Participants' left index finger rested in front of their body midline. Target letters were presented on the screen at all locations tested in the cued blocks. These locations were probed in random order, four times each. The uncued block consisted of 92 trials. This block was performed either before or after the cued blocks, randomized across participants.

### Data Analysis

We calculated the difference in RT for visual discrimination in the presence versus the absence of the cue. The locus of attention was the location with the largest benefit of the cue (the largest decrease in RT in the presence vs. the absence of the cue). The cueing error was calculated as the distance between the locus of attention and the location of the cue (Figure 2).

Cueing error for each cue location was compared before and after cTBS using paired-samples *t* tests. Mean cueing error was analyzed using a repeated-measures ANOVA with factors (1) TMS run (pre vs. post), (2) Stimulation area (S1<sub>EYE</sub> vs. P3), and (3) Gaze direction (leftward vs. rightward). If oculoproprioception is incorporated into attention maps, one would predict a significant three-way interaction, driven by an increased cueing error after S1<sub>EYE</sub>-cTBS. The cueing error was expected to have oppo-

site sign for leftward and rightward gaze, mirroring the underestimation of the angle of gaze after S1<sub>EYE</sub>-cTBS (Experiment 1 in Odoj & Balslev, 2013).

To assess whether the results are robust, we repeated the analysis using a different method for calculating the locus of attention. We now defined the locus of attention as the center of mass of all locations that showed a cueing benefit. First, we identified all locations showing a benefit of the cue, indicated by a faster RT with the cue than without the cue. Then, we calculated the mean of these locations after weighting each location with the magnitude of the cueing effect there. To separate out an eventual practice effect (i.e., an improvement of RT that was common to all target locations within a block), we preprocessed the data by subtracting the mean RT for each block of trials.

### Experiment 2. Visual Map

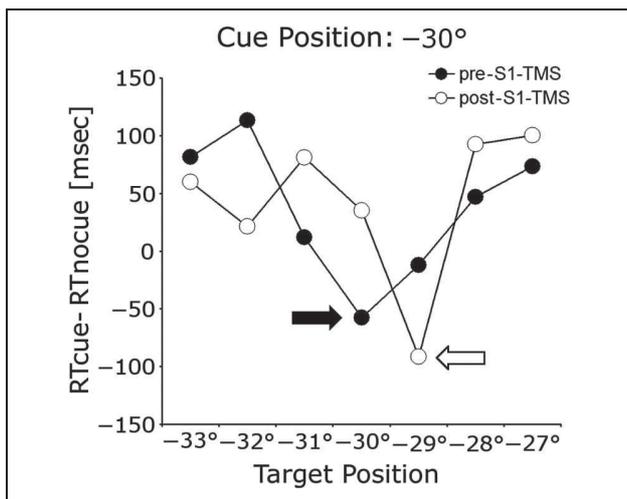
Experiment 2 examined the ability to locate visual targets relative to the left index finger after S1<sub>EYE</sub>-cTBS using a pointing task. This experiment also controlled for an error in hand proprioception after cTBS in the postcentral gyrus, to rule out a systematic error in the perception of the nonvisual cue in Experiment 1.

Participants pointed with their left index finger, the same finger that was used as a nonvisual cue in Experiment 1. Visual targets were presented at the same locations as the cues in Experiment 1. If locating visual targets for reaching takes oculoproprioception into account or if cTBS of the left postcentral gyrus alters perceived posture of the ipsilateral hand, one would expect pointing errors after S1<sub>EYE</sub>-cTBS.

### Setup

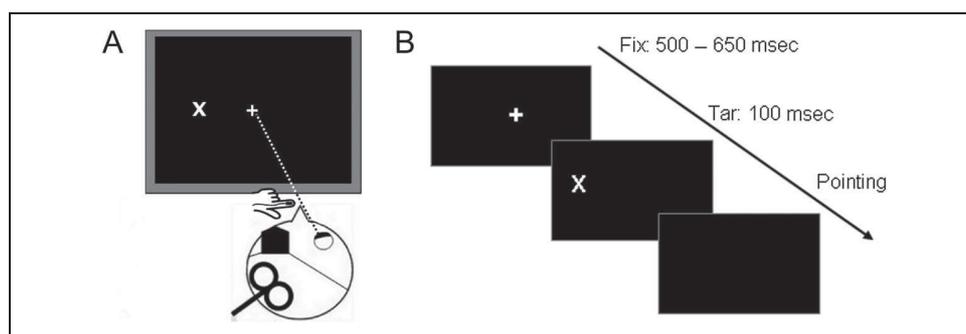
The setup was identical with that used in Experiment 1. Additionally, a position sensor (Polhemus Fastrak, Colchester, VT) was fixed on the tip of the participants left index finger.

At the beginning of the trial, the participants fixated on a central cross (1° × 1°, white on black background). Fixation was verified with the head-mounted eye tracker. Participants' left index finger rested in front of their body midline (Figure 3A). After 500–650 msec (randomized), the fixation cross disappeared. At 100 msec later, a target letter ("X") appeared for 100 msec. The target could appear at four possible locations: at 8°, 18°, 20°, or 30° from orbit midline in Experiment 2A or at -8°, -18°, -20°, or -30° from orbit midline in Experiment 2B. The participants were instructed to close their eyes, then point with their left index finger as accurately as possible at the remembered location of the target. The reaching movement stopped on the wooden ledge when the finger touched the plexiglass. Participants were allowed to adjust the position of their finger until they felt the finger was pointing to the target. After participants confirmed that this was the case, finger position was recorded, and the experimenter moved the finger back to the



**Figure 2.** Cueing error in one example participant with a somatosensory cue at -30° from orbit midline, before and after S1<sub>EYE</sub>-cTBS. Before cTBS over S1<sub>EYE</sub> (●), the largest decrease in RT in the presence versus the absence of the cue occurred for the target that appeared at the same location as the cue (black arrow, cueing error = 0°). After S1<sub>EYE</sub>-cTBS (○), the largest benefit of the cue was observed for the target that appeared at 1° toward the midline (white arrow).

**Figure 3.** Setup and task for the visual open-loop pointing experiment. (A) Participants fixated at  $+19^\circ$  (Experiment 2A) or  $-19^\circ$  (Experiment 2B) from the center of the orbit, while a position marker was attached to their left index finger (here: fixation at  $-19^\circ$ ). (B) A target (letter “X”) was presented for 100 msec at one of four possible positions:  $+8^\circ$ ,  $+18^\circ$ ,  $+20^\circ$ ,  $+30^\circ$  from orbit midline (Experiment 2A) or  $-8^\circ$ ,  $-18^\circ$ ,



– $20^\circ$ ,  $-30^\circ$  from orbit midline (Experiment 2B). After target presentation, participants closed their eyes and pointed to the location where the target appeared. Finger location was recorded, and then the finger was passively moved back to the resting position. The solid line shows eye position at fixation. The dotted line shows perceived gaze direction after S1<sub>EYE</sub>-cTBS according to Odoj and Balslev (2013).

resting position at body-midline. Trials for each target position were grouped in blocks. Each block consisted of six trials. Block order was pseudorandomized.

### Data Analysis

Pointing error was calculated as the signed distance between target and finger location at the end of the movement. Pointing error for each target location was compared before and after cTBS using paired-samples *t* tests. Mean pointing error across all target locations was analyzed using a repeated-measures ANOVA with factors (1) TMS run (pre vs. post), (2) Stimulation area (S1<sub>EYE</sub> vs. P3), and (3) Gaze direction (leftward vs. rightward). If oculoproprioception is incorporated into visual maps, one would predict a significant three-way interaction, driven by an increased pointing error after S1<sub>EYE</sub>-cTBS. The pointing error was expected to have opposite sign for leftward and rightward gaze, mirroring the underestimation of the angle of gaze after S1<sub>EYE</sub>-cTBS (Experiment 1 in Odoj & Balslev, 2013).

### Experiment 3. Perceived Finger Posture

Experiment 1 required to match the position of the unseen finger at rest with a visual target, whereas Experiment 2 asked participants to point the same finger at a visual target without visual feedback. One could explain a systematic cueing error in Experiment 1 despite accurate open-loop pointing in Experiment 2 by an error in the perceived posture of the left index finger at rest. To investigate whether S1<sub>EYE</sub>-cTBS selectively disturbs the felt position of the left index finger at rest (rather than during movement), we conducted a third experiment. In this experiment, participants were asked to point with the left index finger to the remembered position of this finger. The participants had their eyes closed and thus had no visual feedback. We measured pointing error as the difference between the location of finger at the end of movement and the location where the left index finger was passively placed.

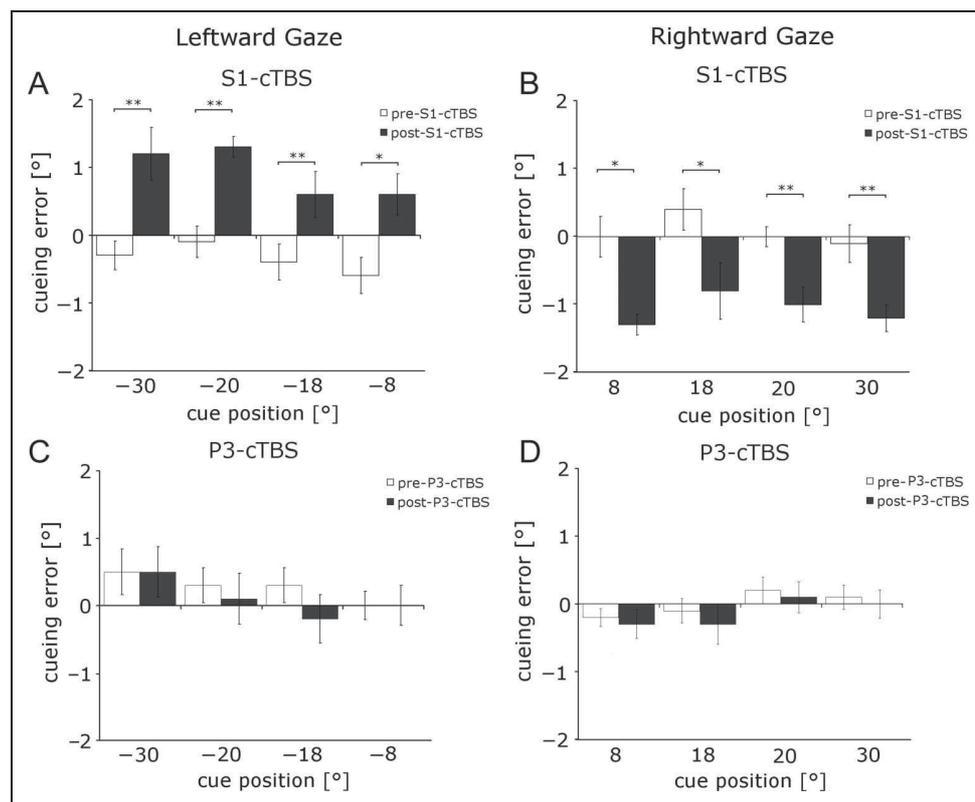
The setup was identical with Experiment 2. At the beginning of each trial, the experimenter took the participant's left index finger from the starting position in front of the body-midline and placed it at one of the four possible locations, identical to the target locations from Experiment 2 and the cue locations from Experiment 1. After 1 sec, the index finger was moved back to start position. Then the participants were instructed to point to the remembered location of their finger as accurately as possible. They confirmed verbally when they reached this location. The experimenter recorded the coordinates of the fingertip and moved the participants' finger back to the start position. Trials for each of the four target position were grouped in blocks. The target was presented six times within one block. The order of the blocks was randomized. If S1<sub>EYE</sub>-cTBS affect perceived position of the left index finger at rest, but not during movement, then one would predict a pointing error in this experiment after S1<sub>EYE</sub>-cTBS.

### TMS

A standard 70-mm-diameter figure-of-eight coil centered over the stimulation site was fixed in place by a coil holder. The participant's head was restrained by a chin rest. We followed an identical procedure for locating S1<sub>EYE</sub> as in previous studies conducted by Balslev and colleagues (Odoj & Balslev, 2013; Balslev, Gowen, et al., 2011; Balslev & Miall, 2008). S1<sub>EYE</sub> was mapped in each participant in relation to the “motor hotspot” of the left hemisphere, which is the scalp projection of the primary motor cortex for the hand (M1). The motor hotspot was defined as the point of maximum evoked motor response in the first dorsal interosseous muscle of the right hand. The S1<sub>EYE</sub> site of stimulation was located at 3 cm posterior to the motor hotspot, measured on a line oriented at  $45^\circ$  from the sagittal plane and perpendicular on the central sulcus.

Post hoc neuronavigation has showed that that this coil location targets an area in the postcentral gyrus, at MNI coordinates (mean  $\pm$  SD:  $-45 \pm 7$ ,  $-32 \pm 7$ ,  $58 \pm 9$ ;

**Figure 4.** Systematic shift in the locus of attention after  $S1_{EYE}$ -cTBS. The locus of attention was defined as the location with the largest benefit of the cue. In leftward gaze, there was a rightward cueing error after  $S1_{EYE}$ -cTBS (A) at all cue locations. This error was specific to  $S1_{EYE}$ -cTBS and did not occur after the stimulation of the control site P3 (C). Likewise, in rightward gaze, there was a leftward cueing error at all cue locations after  $S1_{EYE}$ -cTBS (B) but not after P3-cTBS (D). All values with SEM. \* $p < .05$ , \*\* $p < .01$ , paired-samples  $t$  test.



Balslev, Siebner, Paulson, & Kassuba, 2012). The mean coordinate is associated with a probability of 46% for area 3b, 37% for area 1, and 27% for area 2 according to the probabilistic stereotaxic cytoarchitectonic atlas of the Anatomy Toolbox v2.1 (Eickhoff et al., 2005). The underestimation of the angle of gaze after  $S1_{EYE}$ -cTBS for both left and right directions of gaze (Experiment 1 in Odoj & Balslev, 2013) suggests that  $S1_{EYE}$  is organized like the primary oculoproprioceptive area 3a in the macaque, where neurons encode gaze angle for all directions of gaze (Wang et al., 2007). It is unlikely that TMS applied over the scalp can reach area 3a, located in the depth of the central sulcus (Geyer, Schleicher, & Zilles, 1999). The center-periphery principle of organization, however, may be common to all neural populations that receive an oculoproprioceptive projection. These neural populations are not limited to the depth of the central sulcus but extend into the postcentral and precentral gyri (Balslev, Albert, et al., 2011).

During stimulation, the coil was positioned tangential to the scalp with the long axis of the figure-of-eight coil oriented at  $45^\circ$  to the parasagittal plane. The current flow of the initial rising phase of the biphasic pulse in the TMS coil induced a current flowing from posterior to anterior in the brain. On the basis of the decreased amplitude of the somatosensory-evoked potentials after cTBS over a region situated at 2 cm posterior to M1 (Ishikawa et al., 2007), we assumed that cTBS over  $S1_{EYE}$  results in a decreased excitability of this area. The control site of stimulation in the parietal lobe, P3, was located by using the International

10–20 system for EEG placement. Hilgetag and colleagues found that repetitive TMS over P3 improves visuospatial attention in the ipsilateral hemifield (Hilgetag, Theoret, & Pascual-Leone, 2001). Therefore, we chose this area as control region to check if a possible effect, found in  $S1_{EYE}$ -cTBS, could be explained by a spread of the induced current from  $S1_{EYE}$  toward P3. cTBS consisted of 600 biphasic stimuli produced by a Magstim Rapid<sup>2</sup> stimulator. They were delivered with a frequency of three pulses at 50 Hz repeated at 200 msec (5 Hz) for 40 sec. The stimulation intensity was set at 80% of active motor threshold of the right first dorsal interosseous (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). For each experiment, participants underwent two sessions, with cTBS at either  $S1_{EYE}$  or the control site (P3). The order of the sessions was randomized across participants and scheduled on separate days. During each session, the participant was tested before (pre-cTBS) and after (post-cTBS) on an identical task. Data collection was completed within 13 min after the cessation of the stimulation, a time interval for which the inhibitory aftereffect of cTBS in the somatosensory cortex has been demonstrated (Ishikawa et al., 2007).

#### Eye Tracking

The position of the right eye was recorded with a head mounted tracker that sampled pupil location at 250 Hz. The tracker was calibrated after each cTBS run (pre- or post-cTBS) using a  $3 \times 3$  grid.

Eye position time series were parsed into fixations, blinks, and saccades using the SR EyeLink detection algorithm, which was set to detect saccades with an amplitude of at least  $0.5^\circ$ , using an acceleration threshold of  $9500^\circ/\text{sec}^2$  and a velocity threshold of  $30^\circ/\text{sec}$  and then analyzed offline. Trials with a mean deviation of more than  $1.5^\circ$  from fixation within 50 msec before target presentation were discarded. In Experiment 1, a total of  $10.8 \pm 7.7\%$  (mean  $\pm$  *SD*) trials were discarded. In Experiment 2, a total of  $5.44 \pm 5.28\%$  trials were discarded.

## RESULTS

### Systematic Shift in the Locus of Attention Relative to the Cue after S1<sub>EYE</sub>-cTBS

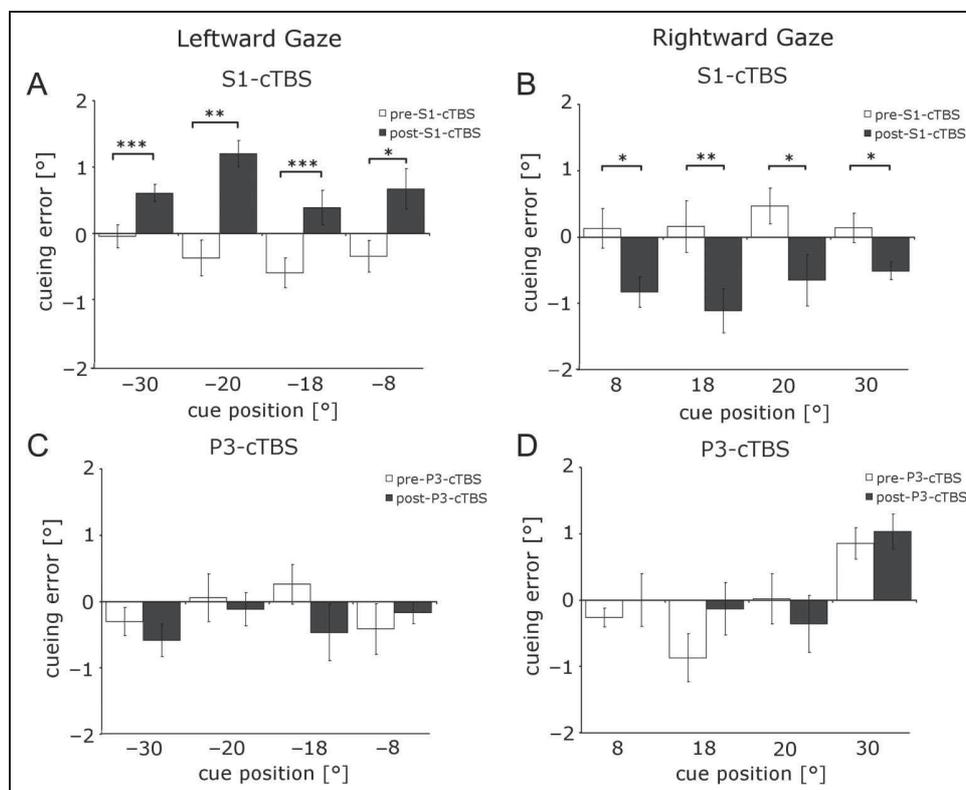
Experiment 1 investigated whether oculoproprioception contributes to locating a nonvisual cue relative to a visual target in a cross-modal attention task. We predicted that, if this is the case, S1<sub>EYE</sub>-cTBS would shift the locus of attention to reflect the bias in the eye proprioceptive signal. In accord with the prediction, after cTBS over S1<sub>EYE</sub> we found a cueing error of  $0.6^\circ$ – $1.3^\circ$  toward the midline (to the right in leftward gaze and to the left in rightward gaze; Figures 4A, B and 6A, B). The cueing error in the post S1<sub>EYE</sub>-cTBS run was significantly different from the pre-cTBS run at all tested cue locations (paired-samples *t* tests: all *p*s < .03). cTBS over P3 did not significantly

change cueing error (Figure 4C and D, paired-samples *t* test: all *p*s > .32). The repeated-measures ANOVA of mean cueing error with factors cTBS run (pre vs. post)  $\times$  Stimulation area (S1<sub>EYE</sub> vs. P3)  $\times$  Gaze direction (left vs. right) showed a significant three-way interaction ( $F(1, 9) = 128.87, p < .001$ ). Both post S1<sub>EYE</sub>-cTBS values were significantly different from pre S1<sub>EYE</sub>-cTBS data (post hoc pairwise multiple comparison using Tukey's test, both *p*s < .01). In comparison, there was no significant change in cueing error after control cTBS over P3 (both *p*s > .05).

A significant interaction was found for Gaze direction  $\times$  cTBS run ( $F(1, 9) = 72.6, p < .001$ ). This interaction was driven by the post-S1<sub>EYE</sub>-cTBS effect in different directions for left and right gaze angles (post hoc pairwise multiple comparison using Tukey's test: *p* < .01 for left post-cTBS vs. right post-cTBS, all other *p*s > .05). None of the other main effects or interactions was significant (all *p*s > .231).

This result was robust across two different methods for identifying the locus of attention. We found the same effect of S1<sub>EYE</sub>-cTBS when the locus of attention was calculated as the center of mass of the locations that showed a cueing benefit. After cTBS over S1<sub>EYE</sub> cueing error was  $0.4$ – $1.2^\circ$  toward center (to the right in leftward gaze and to the left in rightward gaze; Figure 5A and B). The cueing error in the post S1<sub>EYE</sub>-cTBS run was significantly different from the pre-cTBS run at all tested cue locations (paired-samples *t* tests: all *p*s < .04). cTBS over P3 did not change cueing error (Figure 5C and D,

**Figure 5.** Systematic shift in the locus of attention after S1<sub>EYE</sub>-cTBS. The locus of attention was defined as the center of mass of all locations that showed a benefit of the cue. In leftward gaze, there was a rightward cueing error after S1<sub>EYE</sub>-cTBS (A) at all cue locations. This error was specific to S1<sub>EYE</sub>-cTBS and did not occur after the stimulation of the control site P3 (C). Likewise, in rightward gaze, there was a leftward cueing error at all cue locations after S1<sub>EYE</sub>-cTBS (B) but not after P3-cTBS (D). All values with *SEM*. \**p* < .05, \*\**p* < .01, \*\*\**p* < .001 in paired-samples *t* test.



paired-samples *t* test: all *ps* > .21). Repeated-measures ANOVA with factors cTBS run (pre vs. post) × Stimulation area (S1<sub>EYE</sub> vs. P3) × Gaze direction (left vs. right) showed a significant three-way interaction ( $F(1, 9) = 45.9, p < .001$ ). For leftward gaze, the mean cueing error was  $-0.34 \pm 0.3^\circ$  (pre-S1<sub>EYE</sub>-cTBS) and  $-0.1 \pm 0.4^\circ$  (pre-P3-cTBS). For rightward gaze, these values were  $0.2 \pm 0.52^\circ$  for pre S1<sub>EYE</sub>-cTBS and  $-0.07 \pm 0.46^\circ$  for pre P3-cTBS. After S1<sub>EYE</sub>-cTBS, the cueing error was  $0.71 \pm 0.51^\circ$  in leftward gaze and  $-0.78 \pm 0.42^\circ$  in rightward gaze. Both post S1<sub>EYE</sub>-cTBS values were significantly different from pre S1<sub>EYE</sub>-cTBS data (post hoc pairwise multiple comparison using Tukey's test, both *ps* < .02).

Here as well in the previous analysis, a significant interaction was found for Gaze direction × cTBS run ( $F(1, 9) = 19.1, p < .001$ ), driven by the post-S1<sub>EYE</sub>-cTBS effect in different directions for left and right gaze angles (post hoc pairwise multiple comparison using Tukey's test: *p* < .01 for left post-cTBS vs. right post-cTBS, all other *ps* > .05). None of the other main effects and interactions was statistically significant (all *ps* > .115). After P3-cTBS, no significant shift in cueing error could be observed (mean cueing error  $-0.33 \pm 0.56^\circ$  for screen left,  $0.13 \pm 0.52^\circ$  for screen right, post hoc pairwise multiple comparison using Tukey's test: both *ps* > .05).

Participants' accuracy was close to ceiling. They were correct in  $97.85 \pm 1.73\%$  of the trials. We found no differ-

ence in accuracy across conditions. Repeated-measures ANOVA with factors cTBS run (pre vs. post) × Stimulation area (S1<sub>EYE</sub> vs. P3) × Gaze direction (left vs. right) showed no significant three-way interaction ( $F(1, 9) = .276, p = .612$ ). None of the main effects or two-way interactions was significant (all *ps* > .272).

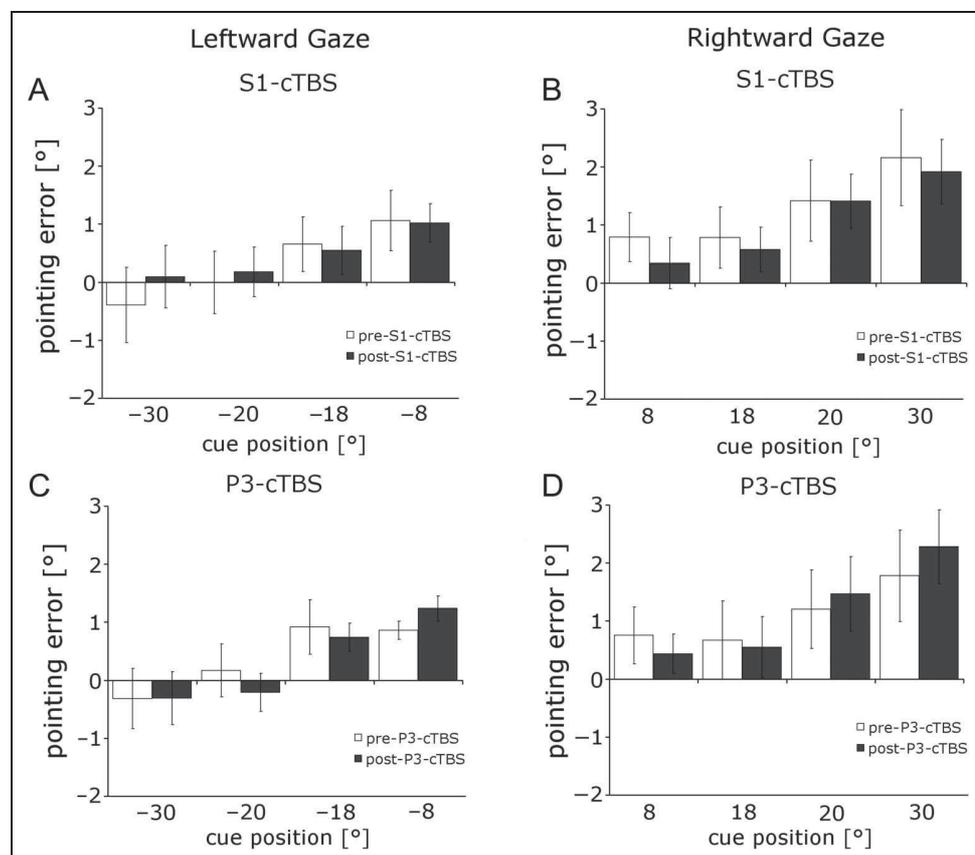
### No Change in Open-loop Pointing to Visual Targets After S1<sub>EYE</sub>-cTBS

Experiment 2 investigated whether S1<sub>EYE</sub>-cTBS impacts the perceived location of visual objects or perceived posture of left hand. If this was the case, one would expect an increase in pointing error after S1<sub>EYE</sub>-cTBS.

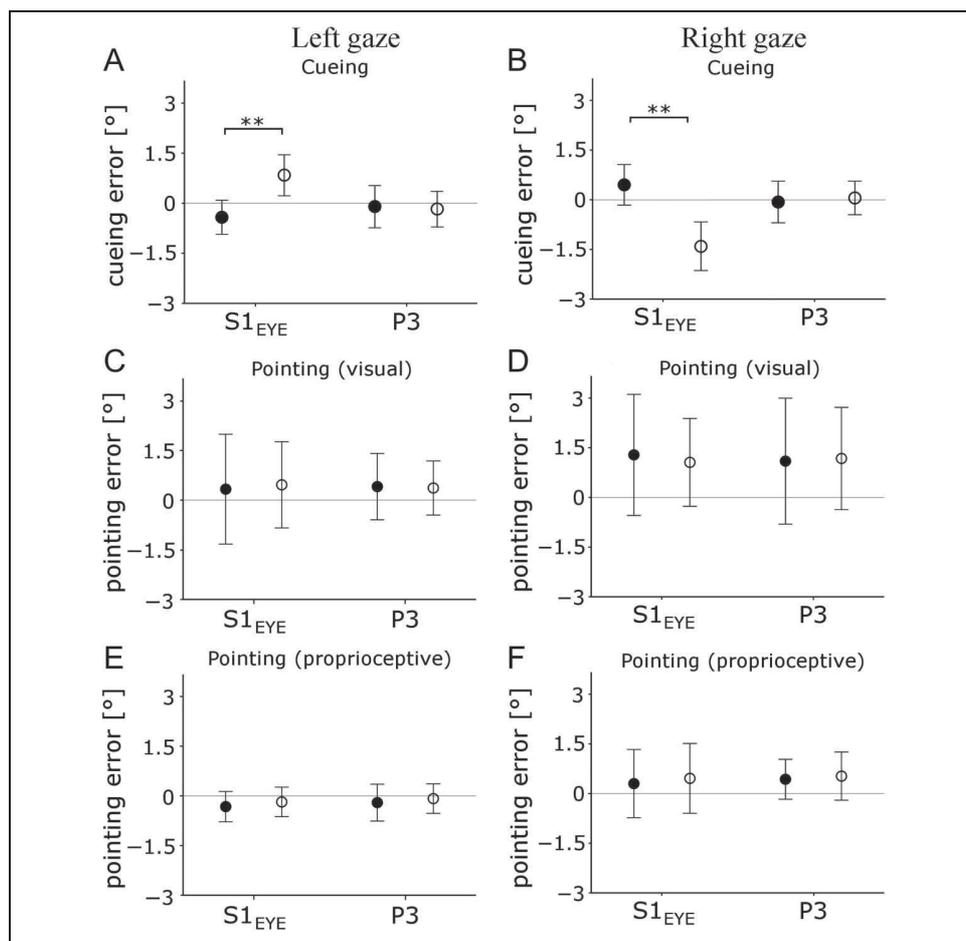
We did not find a statistically significant increase in pointing error for any target position, gaze direction, or stimulation site (Figure 6, paired-samples *t* tests pre- vs. poststimulation, all *ps* > .102). The mean pointing error over all target locations did not change significantly after cTBS (Figure 7C, D). The repeated-measures ANOVA of the pointing error with factors TMS run (pre vs. post) × Stimulation area (S1<sub>EYE</sub> vs. P3) × Gaze direction (left vs. right) showed no significant three-way interaction ( $F(1, 9) = 1.33, p > .27$ ), main effects or two-way interactions (all *ps* > .112).

The precision of pointing was not changed either by cTBS either. The repeated-measures ANOVA with factors

**Figure 6.** No shift in visual pointing for any cueing position after S1<sub>EYE</sub>- or P3-cTBS. In leftward gaze, there was a rightward pointing error after S1<sub>EYE</sub>-cTBS (A). This error was specific to S1<sub>EYE</sub>-cTBS and did not occur after the stimulation of the control site P3 (C). In rightward gaze, there was a leftward pointing error only after S1<sub>EYE</sub>-cTBS (B) but not after P3-cTBS (D). All values with SEM.



**Figure 7.** The effect of S1<sub>EYE</sub>-cTBS is specific for coding the locus of attention. Upper row shows the mean cueing error in the cross-modal attention task for leftward (A) and rightward (B) gaze. The middle row shows the mean error for open-loop pointing to visual targets (C, D), and the lower row shows the pointing error to somatosensory targets (E, F). In the left column, data for left gaze direction are shown; the right column shows data for right gaze direction. Filled circles (●) show pre-cTBS data; empty circles (○) show post-cTBS data. Only changes in cueing error after S1<sub>EYE</sub>-cTBS were significant. All values with 1 SD. \*\* $p < .01$  in post hoc multiple comparison using Tukey's test.



TMS run (pre vs. post)  $\times$  Stimulation area (S1<sub>EYE</sub> vs. P3)  $\times$  Gaze direction (left vs. right) for the *SD* of pointing error showed no significant three-way interaction ( $F(1, 9) = 0.98, p > .32$ ) and no significant main effects or two-way interactions (all  $ps > .181$ ). For left gaze direction, the mean  $\pm$  *SD* of the pointing error across participants was  $0.82 \pm 0.44^\circ$  before S1<sub>EYE</sub>-cTBS and  $0.75 \pm 0.50^\circ$  after S1<sub>EYE</sub>-cTBS. The values for P3-cTBS were  $1.15 \pm 0.48^\circ$  (pre-cTBS) and  $1.01 \pm 0.35^\circ$  (post c-TBS). For right gaze direction, participants had *SD*s of  $1.83 \pm 0.97^\circ$  before S1<sub>EYE</sub>-cTBS and  $1.36 \pm 0.86^\circ$  after S1<sub>EYE</sub>-cTBS. The P3-cTBS values were  $1.53 \pm 0.84^\circ$  (pre-cTBS) and  $1.49 \pm 0.93^\circ$  (post-cTBS).

Direct comparison between the cueing and pointing error in Experiments 1 and 2 using a repeated-measures ANOVA with factors (1) Task (cross-modal attention vs. pointing), (2) TMS run (pre vs. post), (3) Stimulation area (S1<sub>EYE</sub> vs. P3), and (4) Gaze direction (leftward vs. rightward) showed a statistically significant four-way interaction ( $F(1, 9) = 13.327, p < .008$ ). No significant main effects were found (all  $ps > .105$ ). All significant interactions (Task  $\times$  Gaze direction:  $F(1, 9) = 9.99, p = .012$ ; TMS run  $\times$  Gaze direction:  $F(1, 9) = 13.14, p = .006$ ; task  $\times$  TMS run  $\times$  Gaze direction:  $F(1, 9) = 29.67, p < .001$ ; TMS run  $\times$  Stimulation area  $\times$  Gaze direction:  $F(1, 9) =$

$27.18, p = .001$ ) were driven by opposite effect of S1<sub>EYE</sub>-cTBS for different directions of gaze in the cross-modal attention task (post hoc pairwise multiple comparison using Tukey's test:  $p < .01$  for left post-cTBS vs. right post-cTBS and for left post-cTBS vs. right post-cTBS, all other  $ps > .05$ ). A post hoc Tukey's test, comparing pre- vs. post-cTBS, was only significant for pre- vs. post-S1<sub>EYE</sub>-cTBS in the cross-modal attention task for either gaze direction.

### S1<sub>EYE</sub>-cTBS in the Left Hemisphere Does Not Disturb Perceived Position of the Ipsilateral, Left Index Finger at Rest

Experiment 3 controlled for an effect of S1<sub>EYE</sub>-cTBS on felt position of the left index finger at rest. If perceived finger position at rest, but not during pointing, is disturbed by cTBS over S1<sub>EYE</sub>, one would expect an increase in pointing error after S1<sub>EYE</sub>-cTBS here.

We found no significant change in pointing error between pre- and post-cTBS over S1<sub>EYE</sub> or P3 for any of the eight tested locations (paired-samples *t* tests: all  $ps > .106$ ). Repeated-measures ANOVA of mean pointing errors with factors Gaze direction (left vs. right)  $\times$  Stimulation site (S1<sub>EYE</sub> vs. P3)  $\times$  Run (pre vs. post) showed neither main effects nor interactions (all  $ps > .89$ ).

The mean pointing error for each participant before and after cTBS over S1<sub>EYE</sub> or P3 is shown in Figure 7E, F.

## DISCUSSION

We found that altering the activity of an oculoproprioceptive area in the human postcentral gyrus is sufficient to divert attention away from behaviorally important cues. Throughout the visual space, cueing error, or the distance between the cue and the locus of attention, matched well in direction and magnitude the bias in perceived eye rotation measured in a previous study (Odoj & Balslev, 2013). This error cannot be explained by a mislocalization of the visual target. Direct comparison between the attention and reaching tasks (Experiments 1 and 2) showed a significant interaction, driven by the larger error for cross-modal attention than for visually guided reaching. We argue therefore that oculoproprioception is selective for the attention map, as opposed to the visual map for reaching.

Because oculoproprioception was manipulated at cortical level, one could object that the effect of cTBS on attention was merely the result of the disruption of the cortical modules dedicated to this function. This explanation is unlikely. The direction of the cueing error was gaze dependent (leftward in right gaze and rightward in left gaze), and its magnitude at all tested locations matched well the error in perceived eye position (Odoj & Balslev, 2013).

### **A Role of Oculoproprioception in Coding the Locus of Attention Is Compatible with Neurophysiological Data**

Two neural mechanisms have been proposed to implement a locus of attention that anchors retinotopic representations to the physical location of the visual stimuli. First, populations of gain-field neurons with a retinotopic receptive field scale their activity with the angle of gaze to encode visual location relative to the body and/or the world (Pouget et al., 2002; Andersen & Mountcastle, 1983). A second mechanism is remapping of the retinotopic receptive field to account for eye movements (Mirpour & Bisley, 2012; Duhamel et al., 1992). A role of oculoproprioception in coding the locus of attention is compatible with both these mechanisms. A signature of the fastest of the two components of the oculoproprioceptive feedback can be recorded from somatosensory area 3a already at 5 msec before the end of the saccade (Wang et al., 2007). This is in line with the time needed for a remapped representation for the locus of attention to emerge in area LIP at 8–32 msec after the saccade (Mirpour & Bisley, 2012). Likewise, gain-field neurons show ~150 msec postsaccadic delay in updating (Xu, Karachi, & Goldberg, 2012), which is compatible with

the ~60 msec latency of the slower, tonic (Xu et al., 2011) component of the oculoproprioceptive signal.

### **Implications of the Current Findings for Understanding the Coupling between the Eye and Attention**

Although the idea that the eye and attention systems are coupled is not new (Rizzolatti, Riggio, Dascola, & Umiltà, 1987), the mechanism of this coupling remains a current topic of debate (Smith & Schenk, 2012; Wright & Ward, 2008). We argue here that the attention maps incorporate ocular sensory signals to align retinotopic representations to physical locations. A role of the ocular sensory signals in spatial attention is also suggested by observations of a reduced ability to orient attention to cues in patients suffering from a disease of the extraocular muscles or their peripheral innervation (Gabay, Henik, & Gradstein, 2010; Smith, Rorden, & Jackson, 2004; Craighero, Carta, & Fadiga, 2001). Under the assumption that in these patients the brain areas that relay the corollary discharge (Sommer & Wurtz, 2008) are normal, such observations can provide insight into the role of the oculoproprioceptive inflow in spatial attention. Likewise, the allocation of attention is disrupted at extreme rotations of the eyes (Smith, Schenk, & Rorden, 2012; Smith, Ball, Ellison, & Schenk, 2010; Craighero, Nascimben, & Fadiga, 2004), a condition known to cause an abnormal oculoproprioceptive inflow (Paap & Ebenholtz, 1976; Ebenholtz, 1974).

Smith and Schenk have proposed that the oculomotor signals bias the competition among sensory inputs to favor stimuli that are also the end point of a planned saccade (Smith & Schenk, 2012). In line with the idea that attention follows the gaze, can an alternative explanation of the current results be that oculoproprioception merely biases perception to favor visual stimuli nearer the perceived direction of gaze? The design of the spatial attention task rules out this explanation. This is because an unspecific bias toward perceived direction of gaze would have been identical during both conditions, with and without a cue. S1<sub>EYE</sub>-cTBS changed the difference in RT between these two conditions. Thus, cueing error after S1<sub>EYE</sub>-cTBS cannot be explained by a general bias in spatial attention toward the midline.

### **Can the Selective Role of Oculoproprioception in Spatial Attention Be Explained by the Timing of the Underlying Neural Processing?**

Our result is surprising. We found that participants match the same hand location with different retinal locations depending on whether the hand acts as an attention cue or as an effector for action. These results cannot be explained by differences between the attention and pointing task in the timing of the visual target onset. Because of the delay in the ascending pathways,

oculoproprioception can be unreliable for up to 60 msec after an eye movement (Xu et al., 2011; Wang et al., 2007). In both tasks, participants maintained fixation for 600–750 msec before visual target onset. So, it is safe to assume that, at target onset, reliable oculoproprioception had been available. The lack of a detectable effect of the oculoproprioceptive distortion on visually guided reaching is in line with previous findings. Some studies fail to find errors in locating visual targets relative to the body when oculoproprioception is reduced or abnormal (Balslev, Himmelbach, et al., 2012; Lewis et al., 1998) or calculate a smaller weight for oculoproprioception than for the corollary discharge in the multimodal estimate of eye position (Bridgeman & Stark, 1991; Gauthier, Nommay, & Vercher, 1990).

We speculate that the reason for the larger weight of oculoproprioceptive signal from the somatosensory cortex for spatial attention rather than for visually guided reaching is the timing of the underlying neural processes. If neural processing necessary to build attention representations exceeds the time interval in which proprioception is unreliable and if the neural processing for the visual map does not, then only the former would incorporate oculoproprioception. In support of this idea, brain areas that process shape or color (i.e., mainly dedicated to perceptual discrimination) have a longer latency of the visually evoked activity compared with brain areas that process luminance or motion (i.e., mainly for action; Laycock, Crewther, & Crewther, 2007; Schmolesky et al., 1998; Schroeder, Mehta, & Givre, 1998). The longer latency of neural processing for perception versus action may leave more time for computing priority versus reaching maps. The forward model based on the corollary discharge provides an early estimate of eye position that is probably reasonably accurate, given the predictable environment of the orbits. Therefore, fast neural processes (i.e., computing visual maps for reaching) are likely to rely on corollary discharge or, alternatively, on oculoproprioceptive input available upstream the somatosensory cortex. Subcortical structures that could provide oculoproprioceptive signals for visually guided reaching are the superior colliculus, which in rats is connected to the trigeminal nucleus (Ndiaye, Pinganaud, VanderWerf, Buisseret-Delmas, & Buisseret, 2000) or the central thalamus that in the monkey contains neurons sensitive to eye position which discharge after a saccade (Tanaka, 2007). In contrast, neural processes that take longer (i.e., computing the priority map for perception) may accommodate the delay in the ascending proprioceptive pathways and benefit from a more robust estimate of eye position by incorporating the oculoproprioceptive input from the somatosensory cortex.

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**Subject:**

**Bartholomaeus Odoj: Statement from coauthors about PhD- student's contribution to the papers included in the PhD dissertation.**

**Paper 1.** Daniela Balslev, Marc Himmelbach, Hans-Otto Karnath, Svenja Borchers & Bartholomäus Odoj (2012). *Eye proprioception used for visual localization only if in conflict with the oculomotor plan.* *J Neurosci*, 32(25), 8569-8573.

Bartholomaeus Odoj was involved in the development of the idea for this study, contributed to the design of the experiment, collected and analyzed the data and was involved in writing the manuscript.

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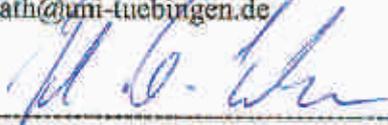


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Svenja Borchers

Process Consulting

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**Subject:**

**Bartholomaeus Odoj: Statement from coauthors about PhD- student's contribution to the papers included in the PhD dissertation.**

**Paper 2.** Bartholomäus Odoj & Daniela Balslev (2013). *Visual sensitivity shifts with perceived eye position.* **J Cogn Neurosci**, 25(7), 1180-1189.

Bartholomaeus Odoj was involved in the development of the idea for this study, contributed to the design of the experiment, collected and analyzed the data and was the main author involved in writing the manuscript.

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**Subject:**

**Bartholomaeus Odoj: Statement from coauthors about PhD- student's contribution to the papers included in the PhD dissertation.**

**Paper 3.** Daniela Balslev, Bartholomäus Odoj, & Hans-Otto Karnath (2013). *Role of somatosensory cortex in visuospatial attention.* *J Neurosci*, 33(46), 18311-18318.

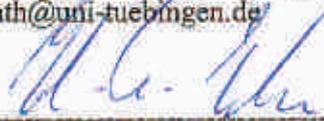
Bartholomaeus Odoj was involved in the development of the idea for this study, contributed to the design of the experiment, collected and analyzed the data and was involved in writing the manuscript.

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**Subject:**

**Bartholomaeus Odoj: Statement from coauthors about PhD- student's contribution to the papers included in the PhD dissertation.**

**Paper 4.** Bartholomäus Odoj & Daniela Balslev (2015). *Role of oculoproprioception in coding the locus of attention.* (in press, **J Cogn Neurosci**)

Bartholomaeus Odoj was involved in the development of the idea for this study, contributed to the design of the experiment, collected and analyzed the data and was the main author involved in writing the manuscript.

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