Graduate School of
Systemic Neurosciences
LMU Munich

Subjective orientation perception in hemispatial neglect:

Effects of internal and external mediators of subjective space perception

and of feedback-based perceptual training

Dissertation

at the Graduate School of Systemic Neuroscience

Ludwig-Maximilian-University Munich

Submitted by

MSc Johanna Funk

from Munich, Germany

Munich, January 2012

Supervisors: Dr. Kathrin Finke

Prof. Dr. Hermann Müller

Tag d. mündl. Prüfung : 21.05.2012

Declaration

I hereby confirm that this work submitted for assessment „Subjective orientation perception in hemispatial neglect: Effects of internal and external mediators of subjective space perception and of feedback-based perceptual training" is my own and is expressed in my own words, except where otherwise stated. Any uses made of the work of other authors (e.g., ideas, findings, tests, text) are properly acknowledged at the point of their use. A full list of the references employed has been included.

This dissertation has not already been accepted for any degree, and is also not being concurrently submitted for any other degree.

Munich, January 2012

Johanna Funk

Acknowledgements

This dissertation would not have been written without the contribution of many people. I am very grateful for that, and I thank the people who contributed directly to my PhD project, or who provided logistic help, support and encouragement.

My deepest gratitude is to my first advisor, Dr. Kathrin Finke who supported me during the whole PhD period, and on each individual level of my work. Kathrin already accompanied my university career from the first semester on and was one of the teachers who deepened my interest in cognitive Neuroscience. I have been fortunate to have an advisor who gave me freedom and encouragement to explore things on my own, and at the same time her competent guidance wherever necessary. Her patience and support helped me to overcome many difficult situations and finish this dissertation.

I am grateful to my second advisor, Prof. Dr. Hermann Müller, for supporting me during my Master and PhD studies. He accepted me as a student of the Neuro-cognitive Psychology masters program, which deepened my knowledge in cognitive Neuroscience and research methods and finally paved the way to my PhD project. I would like to thank Hermann for his insightful comments and constructive advice at various stages of my studies and research.

Prof. Dr. Georg Kerkhoff, my external advisor and mentor accompanied my university career from my first semester until today. His infectious enthusiasm for his research field inspired me to delve more deeply into the subject of cognitive Neuroscience. Georg supervised my first research project and my diploma thesis and encouraged me to apply for the Neuro-cognitive Psychology program. He accompanied my studies and research in a supportive and encouraging way and gave me great and invaluable support for my PhD project.

I am grateful to my colleagues from the Neuropsychology and the General and Experimental Psychology Unit for their company, and innumerable enriching discussions and relieving conversations. Furthermore I would like to thank the past and present members of the Graduate School of Systemic Neuroscience for their help and support, especially the coordinators Dr. Alexandra Stein and Lena Bittl who were very patient and helpful in answering my questions. I am thankful to Prof. Dr. Brandt, who was a member of my thesis advisory committee and contributed interesting ideas and constructive advice during the committee meetings.

I would like to acknowledge my external collaborators, Kathrin Utz, Silvia Sollfranck, Stefan Reinhart, Mareike Kardinal, Alisha Rosenthal and Caroline Kuhn, for contributing to my research or revising my manuscripts. I am furthermore grateful to Rudolf Preger from the neurological clinic Kipfenberg for the permission to recruit patients, and Günter Neumann from Kipfenberg and Udo Münßinger from the Hospital Bogenhausen for their support in the recruitment of patients.

Most importantly, none of this would have been possible without the patience of my family, who has been a constant source of support and strength during the last years. I would like to express my gratitude to my parents for their encouragement and financial support and to my husband and daughter who anchored me in many situations.

Finally, I highly appreciate the financial support from the Graduate Program of the LMU and the Graduate School of Systemic Neuroscience, who funded my research.

List of publications

Funk, J., Finke, K., Mueller, H.J., Preger, R., & Kerkhoff, G. (2010a). Systematic biases in the tactile perception of the subjective vertical in patients with unilateral neglect, and the influence of upright vs. supine posture. *Neuropsychologia, 48(1),* 298-308.

Funk, J., Finke, K., Mueller, Utz, K.S., & Kerkhoff, G. (2010b). Effects of lateral head inclination on multimodal spatial orientation judgments in neglect: Evidence for impaired spatial orientation constancy. *Neuropsychologia, 48(6),* 1616-1627.

Funk, J., Finke, K., Mueller, H.J., Utz, K.S., & Kerkhoff, G. (2011). Visual context modulates the subjective vertical in neglect: Evidence for an increased Rod-and-Frame-Effect. *Neuroscience, 173,* 124-134.

Funk, J., Finke, K., Reinhart, S., Kardinal, M., Utz, K.S., Rosenthal, A., Kuhn, C., Müller, H.J., & Kerkhoff, G. (submitted). Effects of feedback-based visual line orientation discrimination training in visuospatial disorders after stroke. *Neurorehabilitation and Neural Repair.*

Abstract

Patients with right hemisphere lesions and spatial hemi-neglect display deficits beyond the typical neglect and extinction symptoms observed in the horizontal plane. Studies investigating deficits in the frontal and sagittal plane revealed impairments in the judgment of the subjective vertical, horizontal and oblique orientations. Systematic counterclockwise deviations in subjective verticality and orientation perception have been demonstrated in the visual and tactile modality, indicating a supramodal spatial orientation deficit. The magnitude of such deviations was shown to be modulated by internal factors mediating subjective space perception. The present study investigated whether and how spatial orientation deficits are modulated (1) by further internal and external, contextual changes in neglect patients and (2) by perceptual orientation discrimination training. In four experiments, we analyzed effects of body posture (upright vs. supine), passive lateral head inclination (clockwise vs. counterclockwise), visual contextual information (no vs. upright vs. tilted context) and repetitive feedback-based orientation discrimination training on biases in spatial orientation perception. Our data showed that neglect patients generally displayed a marked variability as well as a systematic tilt in their spatial judgments. In line with the assumption of a multimodal and multispatial deficit, their subjective vertical and horizontal was biased in the visual and in the tactile modality and in the frontal and sagittal plane. Furthermore, manipulations of internal and external mediators of subjective space perception systematically modulated the performance of neglect patients. They displayed deteriorated performance in supine compared to upright posture, an enhanced ‘A-effect’ (i.e., a modulation of orientation judgements in the direction of head tilt) as well as an increased rod-and-frame-effect (i.e., a modulation of orientation judgements as a function of frame tilt). This dramatically enhanced modulability might be caused by a pathologically increased influence of internal and contextual cues on

subjective space perception in neglect patients as a consequence of impaired processing of gravitational information. The results indicate a loss of spatial orientation constancy which leads to an increased reliance on any cues mediating subjective space perception in neglect. With regard to the effectiveness of repetitive feedback-based orientation discrimination training, we found rapid improvements in trained but also in non-trained spatial orientations after training in all patients, stability of improvements at 2-months follow-up, and graded transfer of improvements to related visuospatial tasks. These results show a considerable potential for treatment-induced improvements in visuospatial deficits following perceptual, feedback-based training of visual line orientation which might be used for a better treatment of spatially impaired stroke patients. In summary, we showed (1) that neglect patients display a systematic bias of spatial orientation perception along with a loss of spatial orientation constancy, and (2) that both the bias and the uncertainty in subjective space perception can be reduced by feedback-based perceptual training.

Table of Contents

Acknowledgements....iii

List of publications....v

Abstract....vi

Table of contents....vii

Chapter 1: General Introduction....1

1.1. Cortical pathways for visual perception: The dorsal and ventral visual system....2

1.1.1. Differential views on the dorsal visual system....3

1.1.2. Space processing and multimodal integration in parietal cortex....4

1.1.3. Orientation representation in parietal cortex....6

1.2. Neuropsychological disorders after parietal lesions....7

1.2.1. Visuospatial Disorders....8

1.2.2. Hemispatial Neglect....9

1.2.3. Deficits in subjective verticality perception....11

1.3. Rationale of the project....13

1.3.1. Hypotheses....14

1.4. References....17

Chapter 2: Studies on individual research questions....25

2.1. Systematic biases in the tactile perception of the subjective vertical in patients with unilateral neglect, and the influence of upright vs. supine posture....26

2.1.1. Abstract....27

2.1.2. Introduction....28

2.1.3. Methods....34

2.1.4. Results....39

2.1.5. Discussion....46

2.1.6. References....55

2.2. Effects of lateral head inclination on multimodal spatial orientation judgments in neglect: Evidence for impaired spatial orientation constancy....61

2.2.1. Abstract....62

2.2.2. Introduction....63
2.2.3. Methods....70
2.2.4. Results....76
2.2.5. Discussion....87
2.2.6. References....95

2.3. Visual context modulates the subjective vertical in neglect: Evidence for an increased Rod-and-Frame-Effect....101

2.3.1. Abstract....102
2.3.2. Introduction....103
2.3.3. Methods....109
2.3.4. Results....115
2.3.5. Discussion....120
2.3.6. References....128

2.4. Effects of feedback-based visual line orientation discrimination training in visuospatial disorders after stroke....133

2.4.1. Abstract....134
2.4.2. Introduction....135
2.4.3. Methods....138
2.4.4. Results....145
2.4.5. Discussion....150
2.4.6. References....154

Chapter 3: General Discussion....159

3.1. Synopsis of results....160

3.2. Evidence for a supramodal orientation deficit in neglect....161

3.2.1. Impaired spatial orientation constancy in neglect....162

3.3. Putative mechanisms of plasticity following visuospatial training....164

3.3.1. Clinical relevance of training and transfer effects....165

3.4. Conclusion....166

3.5. Future directions....167

3.6. References (General Introduction and Discussion)....169

Chapter 1: General Introduction

1.1. Cortical pathways for visual perception: The dorsal and ventral visual system

Several decades ago, evidence from neurobehavioral, physiological and anatomical studies (for review, see Ungerleider & Mishkin, 1982) in the macaque monkey established the idea of two separate cortical visual pathways that can be distinguished structurally and functionally, one being specialized for object vision and the other for spatial vision. Subsequent clinical and functional imaging studies (for review, see e.g. Ungerleider et al., 1998) in humans confirmed this idea of two anatomically and functionally specialized, but at the same time closely connected visual projection systems, the dorsal and ventral route of visual processing. Both systems are organized in specialized but interacting modules and ascend from cortical area 17 (V1, primary visual cortex) to extrastriate cortical visual areas in the temporal and parietal lobes and finally to regions in the frontal cortex relevant for object-specific or visuospatial working memory processes (e.g., Courtney et al., 1996; Ungerleider et al. 1998). The ventral or occipito-temporal projection system (the so-called 'what' pathway) is suggested to be specialized for object perception and recognition including the analysis of e.g. form and color, the dorsal or occipito-parietal system (the so-called 'where' pathway) is suggested to be specialized for spatial perception including the analysis of e.g. depth, position and orientation (e.g., Haxby et al., 1991; Mishkin et al., 1983; Ungerleider & Haxby, 1994; Ungerleider & Mishkin, 1982). Evidence from lesion studies in nonhuman primates showed that lesions of inferior temporal cortex cause severe deficits in performance on several visual discrimination tasks (e.g., pattern, object, and color), but not on visuospatial tasks, whereas posterior parietal lesions cause severe deficits in visuospatial performance but do not affect visual discrimination performance (e.g., Pohl, 1973; for review, see Ungerleider & Mishkin, 1982). Accordingly, physiological evidence showed that cells in areas within the ventral pathway respond to visual features relevant to object identification (e.g., color, texture, and shape), whereas cells in areas within the dorsal pathway respond to spatial aspects of stimuli (e.g., position, orientation, motion direction and velocity, for reviews, see e.g. Desimone & Ungerleider, 1989; Maunsell & Newsome, 1987). Clinical studies in brain-damaged patients have shown that also in humans, there are specific clinical syndromes produced by occipitotemporal and occipitoparietal lesions depending on the respective module damaged by the lesion. Syndromes occurring after occipitotemporal lesions include e.g. visual object agnosia, prosopagnosia, and achromatopsia (e.g., Newcombe et al., 1987; for review, see Farah, 2004), whereas those occurring after occipitoparietal lesions include e.g. visuospatial neglect, apraxia, optic ataxia, akinotopsia, and disorders of spatial perception and cognition (e.g., Eglin et al., 1989; Vaina et al., 1990; Zihl et al., 1991; for review, see Newcombe & Ratcliff, 1989).

1.1.1. Differential views on the dorsal visual system

A re-interpretation of the two visual systems by Goodale and Milner (Goodale & Milner, 1992; Milner & Goodale, 2008) suggests that the two streams are not only specialized with regard to the kind of information they process, but rather with regard to the purpose of information processing: they assume that in the ventral stream, information about a range of object parameters is transformed for perceptual purposes, whereas in the dorsal stream (some of the same and some different) object parameters are transformed for the control of actions. In this view, the parietal cortex is processing visuospatial information for mediating visually guided (e.g., grasping) movements, but not visuospatial perception for recognition.

However, patients with parietal damage clearly demonstrate visuospatial impairments that cannot be attributed to visuomotor defects. For example, Cramon and Kerkhoff (1993) showed that patients with focal parietal lesions demonstrate impaired perception of horizontal and vertical axes, deficits in length and distance estimation, and deficits in orientation discrimination and position matching. Therefore, although visuospatial deficits after parietal damage are often accompanied by visuomotor impairments, they cannot be fully accounted for by them.

On the basis of new anatomical data as well as a reconsideration of functional and clinical data, Rizolatti and Matelli (2003) tried to integrate the different views on the the functional role of the dorsal visual stream and proposed that the dorsal stream (and its recipient parietal areas) form two distinct functional systems: the dorso-dorsal stream, serving the 'on-line' control of actions, and the ventro-dorsal stream involved in space perception and the understanding of actions. Reviewing recent imaging and lesion studies, Husain and Nachev (2007) argued that inferior parietal regions (that were typically suggested to contribute to vision-for-action and/or spatial functions) also have non-spatial functions which are neither 'dorsal' nor 'ventral' in nature, such as sustaining attention or detecting salient events. Considering the diversity of functions attributed to the dorsal stream and its associated brain areas, it still remains necessary to further specify the construct 'dorsal stream' and the neuroanatomy underlying the specific sub-modules of this construct.

1.1.2. Space processing and multimodal integration in parietal cortex

Research in nonhuman primates has shown that the dorsal projection system starts with striate and V2 projections to visual area V5 or MT (medial temporal), located in the caudal portion of the superior temporal sulcus (STS), which separates the occipital and parietal lobes (for reviews, see Ungerleider & Haxby, 1994; Ungerleider et al., 1998). Area MT in turn projects to further areas in the upper superior temporal sulcus (MSTd and MSTl, the dorsal and lateral part of the medial superior temporal area) and the intraparietal sulcus which subdivides the posterior parietal cortex into two main sectors, the superior parietal lobule (SPL; e.g., VIP and MIP, ventral and medial intraparietal cortex) and the inferior parietal lobule (IPL; e.g., AIP and LIP, anterior and lateral intraparietal cortex). Each of these areas can be seen as a submodule of visuospatial perception which is highly specialized for the processing of clearly defined aspects of spatial information (for reviews, see e.g., Colby & Goldberg, 1999; Rizolatti & Matelli, 2003), including different aspects of motion processing (MT and MST), extrapersonal (MIP) and peripersonal / perioral (VIP) spatial information processing, and eyemovement- (LIP) or grasp-related spatial representation (AIP).

Albeit this high degree of specialization, cells within the dorsal pathway do not only correspond with other cells within this pathway, but also with cells processing information from other (than the visual) modalities. Both SPL and IPL have been shown to receive inputs from the visual and the somatosensory cortices (e.g., Colby & Duhamel, 1991). Moreover, research has shown that neurons in the posterior parietal cortex are multimodal themselves, i.e., they contribute to the representation of space by integrating multimodal afferent and efferent / reafferent information (Andersen et al., 1985). For example, neurons in MIP (specialized for responding to stimuli within reaching distance) exhibit a range of response properties from purely visual, to bimodal, to purely somatosensory (Colby & Duhamel, 1991). Parietal areas 7a and LIP have been shown to receive visual signals and eye position signals (Andersen & Mountcastle, 1983; Andersen et al., 1985) as well as efference copies of motor signals, vestibular signals and neck proprioceptive signals (e.g. Bremmer et al., 2002; Brotchie et al., 1995; Snyder et al., 1997) to account for head orientation and head movements in space. Damage to the (right) posterior parietal cortex might therefore lead to a systematic gain-error in the integration of information – as for example visual, somatosensory (head-position) and graviceptive / vestibular input. The specialization on several aspects of visuospatial processing along with the integration of multimodal afferent and reafferent information support the role of the posterior parietal cortex as the anatomical substrate of a supramodal spatial reference frame.

1.1.3. Orientation representation in parietal cortex

The assumption of the parietal cortex as the anatomical substrate of a supramodal spatial referece frame is supported by findings indicating the existence of multimodal (e.g. Duhamel, et al., 1998; Graziano & Gross, 1995) and 'axis-orientation-selective' (Sakata et al., 1997) neurons in the parietal cortex. Based on single-cell recordings in the monkey parietal cortex, Sakata et al. (1997; 1999) identified neurons in the lateral bank of the caudal intraparietal sulcus and in the anterior intraparietal sulcus which are sensitive to orientation information, though these cells might support different aspects of orientation perception with regard to intentional orientation discrimination as opposed to the visual guidance of hand actions. In humans, lesion and imaging studies support the view that the (right) parietal cortex plays a dominant role in spatial orientation perception, but also indicate that several brain regions contribute to visual orientation discrimination. Early patient studies reported that deficits in visual orientation discrimination frequently occur after right hemisphere lesions, typically affecting the (temporo-) parietal lobe and/or the basal ganglia, less frequently also after left frontal lesions (Benton et al., 1975; Kim et al., 1984). A recent patient study analyzing the lesion sites critical for line orientation discrimination showed that failure was most strongly associated with lesions in the right posterior parietal region (Tranel et al., 2009).

Imaging studies support the view that the right parietal cortex is crucial for spatial orientation perception (Ng et al., 2000; Sack et al., 2001; Taira et al., 1998), but also indicate that other brain regions also contribute to visual orientation discrimination, including including V1, the lateral occipital cortex, superior temporal cortex, and also subcortical structures (e.g., Vandenberghe et al., 1996). Furthermore, evidence from fMRI studies showed that parietal cortex activation in orientation-related tasks depends on the type of orientation information which is currently processed. The anterior intraparietal sulcus seems to be particularly activated during orientation discrimination (e.g., Faillenot et al., 2001). Shikata et al. (2003)

demonstrated that the caudal part of the intraparietal sulcus was activated more strongly in an orientation discrimination task than when surface orientation was used to guide reaching. Based on these findings and on their own observations in patients with parietal damage, Riddoch et al. (2004) proposed that orientation information is coded by different brain areas in parallel, but for different purposes. They suggest that the ventral system is concerned with an implicit coding of orientation into shapes (for pattern recognition) while the dorsal system is concerned with a more explicit coding of orientation.

1.2. Neuropsychological disorders after parietal lesions

While smaller and well defined lesions of the (right) occipitoparietal cortex can lead to quite circumscribed deficits in visual processing (e.g., akinotopsia or motion blindness, which occurs after V5 / MT lesions), most patients with MCA (middle cerebral artery) infarctions leading to large right hemispheric lesions including the parietal lobe show several disorders simultaneously. Frequently, visuospatial and -constructive disorders occur together with visuospatial neglect, spatial-attentional disorders and anosognosia, the unawareness for all of these deficits (e.g., Karnath & Rorden, in press; Kerkhoff, 1998). Since these disorders overlap and interact, it is often difficult to disentangle them. Nevertheless, different mechanisms of space processing in the human parietal lobes have been suggested on the basis of disorders occurring after parietal lesions and the superior and inferior parts of the parietal lobe have been assigned distinct functional properties. In their above-mentioned theory of the visual system, Milner and Goodale (1995) suggested that the superior parietal lobe is part of the dorsal stream of visual processing and its input transformations mediate the control of goal-directed actions. Similarly, Perenin (1997) supports the view that the superior part of the parietal cortex is mainly involved in the direct coding of space for action, whereas he argues that the inferior part is responsible for conscious representations underlying spatial cognition and awareness. Accordingly, lesions restricted to the superior part in humans therefore often lead to disturbances of visuomotor control (such as optic ataxia). On the other hand, spatial neglect was attributed to lesions of the inferior part of the parietal lobe which is assumed to deal with abstract spatial processing based on input from the ventral stream, allowing the formation of perceptual and cognitive representations. However, the basic pathophysiological principles leading to spatial neglect are still an issue of debate. In an effort to resolve this debate, Karnath (1997) suggested that exploratory and goal-directed behavior in space do not share the same neural mechanisms. Karnath argued that space representation in the inferior parietal lobe most probably serves as a matrix for spatial exploration and orienting in space whereas visuomotor processes (involved e.g. in reaching for objects) are rather located in the superior parietal lobe. Accordingly, spatial neglect would typically occur after inferior parietal lesions, while optic ataxia would typically occur after superior parietal lesions. Although there is converging evidence for the anatomical dissociations within the parietal lobe, critical lesion sites inducing spatial neglect remain debated (see literature reviewed below). Since spatial neglect is characterized by a large heterogeneity in clinical manifestations, which overlaps with or comprises visuospatial and –constructive deficits, hemispatial neglect and visuospatial disorders are even more difficult to disentangle. Therefore, the criteria for diagnosing neglect and for differentiating between neglect and other, e.g. visuospatial, disorders have been challenged by some authors recently (e.g., Karnath & Rorden, in press).

1.2.1. Visuospatial Disorders

Right-hemispheric brain damage (RBD) is frequently accompanied by profound visuospatial and visuoconstructive disorders (Hier et al., 1983; Jesshope et al., 1991; Meerwaldt et al., 1982). Lesions of extrastriate cortical and subcortical structures, e.g., parietal, temporo-parietal, thalamic or basal ganglia lesions of the right (50-70%) or more rarely also the left hemisphere (30-50%; Jesshope et al., 1991) lead to impairments in the perception of visual space as well as acting and orienting in space. Typically, right hemisphere lesions cause not only more frequent, but also more severe deficits compared to left hemisphere lesions (e.g., Kim et al., 1984). Deficits RBD patients show include line orientation judgements (Benton et al., 1975; De Renzi et al., 1971; Kim et al., 1984), line bisection / subjective straight ahead (e.g., Ferber & Karnath, 1999), size, distance and position estimation (e.g., Milner & Harvey, 1995; Tartaglione et al, 1981, 1983), clock reading / drawing (Freedman et al., 1994), and block design performance (Young et al., 1983).

After large MCA infarctions, visuospatial and -constructive disorders often occur simultaneously with spatial neglect. However, the two disorders can also occur independently of each other. Visuospatial disorders (and also spatial neglect) are often accompanied by substantial deficits in mobility and ADL functions (activities of daily living), e.g. dressing or transfer from bed to chair (Jesshope et al., 1991; Kaplan & Hier, 1984). Furthermore, these deficits are significant predictors of the course of disease, as they show adverse effects on therapy outcome of the patients and, thus, delay and impair their recovery. Patients with large, right hemispheric lesions show the poorest outcome in neurorehabilitation, which is at least partly due to anosognosia, the unawareness of the deficits. Anosognosia is an essential problem for the therapeutic success, since it is often little noticed but associated with problems in ADL functions. Therefore, information about the quality and magnitude of the visuospatial disorder is of great importance in the therapy of such disorders.

1.2.2. Hemispatial Neglect

Hemispatial neglect is a supramodal neurological disorder characterized by a complex syndrome of sensory, motor and representational deficits (for review, see Kerkhoff, 2001). Neglect patients fail to detect or respond to stimuli in their contralesional hemispace (Bisiach et al., 1996), show unilateral spatial representational deficits (Bisiach & Luzatti, 1978; Bisiach et al., 1981) and frequently display a reduced use of their contralesional extremities (Laplane & Degos, 1983). Most of the current models of neglect focus on the explanation of deficits in the horizontal plane. Such deficits are apparent, for example, as left-sided omissions in visual search, reading, writing and drawing tasks, as deficits in (horizontal) size perception in the contralesional hemispace (Milner & Harvey, 1995; Milner et al., 1993), as a compression of contralesional hemispace (Gainotti & Tiacci, 1971; Nichelli et al., 1989) or even both hemispaces (Halligan & Marshall, 1991), as rightward deviations in line bisection and in pointing straight ahead, and as a deviation of space representation toward the ipsilesional hemispace (Karnath, 1997). However, numerous studies have demonstrated deficits in visuospatial perception and visuomotor performance that cannot result solely from impairments restricted to the horizontal plane. These include impairments in visual orientation discrimination and position estimation (Tartaglione et al., 1981, 1983; Taylor & Warrington 1973; Warrington & James 1967) as well as deficits in the judgment of the subjective visual vertical (SVV) and horizontal (SVH; Howard, 1982; Lenz, 1944), and judgments of oblique line orientations (Benton et al., 1975; De Renzi et al., 1971; Kim et al., 1984).

Lesions sites which have been observed to cause hemispatial neglect include the insula (Karnath et al., 2004), the temporo-parietal junction (e.g. Vallar & Perani, 1986), posterior parietal (e.g. Mesulam, 1999) and intraparietal cortices (Mort et al. 2003), and the superior temporal gyrus (e.g., Karnath et al., 2001, 2004) at the cortical level as well as the thalamus and basal ganglia areas (Karnath et al., 2004; Vallar & Perani,1986) at the subcortical level. Since hemineglect is characterized by a large heterogeneity in clinical manifestations, it is not surprising that multiple lesion sites have been associated with neglect (for review, see Karnath & Rorden, in press). Due to this multi-componential nature of the neglect syndrome, recent research on the neuroanatomy of neglect now refrained from trying to identify 'the' anatomical correlate of spatial neglect (as a consistent and uniform disorder), but rather started to identify dissociable functional components of the disorder and their anatomical correlates. In a recent pioneer study, Verdon et al. (2010) identified coherent profiles of co-varying deficits in a statistical factorial analysis of neglect performance and examined the neural correlates of these distinct profiles using a statistical voxel-based lesion-symptom mapping method. This analysis revealed three main factors (explaining 82% of the variance) suggesting distinct components related to perceptive/visuo-spatial, exploratory/visuo-motor, and allocentric/object-centred aspects of spatial neglect which were linked to specific neural correlates for each component, including the right inferior parietal lobe, the right dorsolateral prefrontal cortex, and deep temporal lobe regions. If such a multi-componential model of neglect based on factorial analyses proves valid in further studies, future research might not deal with ‚the' neglect syndrome in the current sense any longer.

1.2.3. Deficits in subjective verticality perception

Despite the above-mentioned heterogeneity of neglect symptoms, there appear to be deficits which can be found in most patients. Systematic tilts in subjective verticality and orientation perception seem to be such a deficit which occurs in nearly all neglect patients. The relation between brain damage and deviations of the subjective vertical was studied already many decades ago (e.g., Bender & Jung, 1948), but has been linked to spatial neglect only recently (Kerkhoff & Zoelch, 1998; Kerkhoff, 1999; Yelnik, 2002). Early studies (e.g., Bender & Jung, 1948) found that deviations of the subjective vertical from the true vertical are indicative of frontal or parietal, but not of occipital lobe lesions. The direction of the deviations was reported to be contralesional, with clockwise (CW) deviations following left, and counterclockwise (CCW) deviations following right fronto-parietal lesions. In a large-scale investigation, Brandt et al. (1994) tested judgements of the SVV in 71 patients with unilateral hemispheric lesions. MRI analyses revealed that the most impaired patients had lesions centering on the human homologue of the monkey parieto-insular-vestibular cortex (PIVC; Grüsser et al., 1990). In a recent study with 80 stroke patients, Pérennou et al. (2008) found that patients with right hemisphere lesions showed CCW visual (in 55% of the subjects), tactile (32.5%) and postural (42%) tilts in the frontal plane. Since especially parietal lesions caused marked visual and tactile tilts in the frontal plane, the authors concluded that the right parietal cortex is crucially involved in the elaboration of an internal supramodal model for verticality perception.

Considering that lesion sites related to deviations of subjective space perception are neighbouring and overlapping with those known to cause the neglect syndrome, it is not astonishing, that neglect patients present not only with a displacement of an egocentric reference frame to the ipsilesional side of space but also with abnormal visuospatial judgements, that is, CCW tilts of axes in the vertical, horizontal, and oblique orientation in the frontal plane (Kerkhoff & Zoelch, 1998). As in the horizontal plane, these deficits in the frontal plane are multimodal as they occur in both the visual and tactile modality, with the deviation in both modalities being correlated with each other and with the neglect severity (Kerkhoff, 1999; Utz et al., 2011). Importantly, this multimodal deficit is not an unspecific consequence of brain damage, but appears to be specifically related to spatial neglect, as patients with left- or right-hemispheric lesions *without* neglect usually perform at the level of healthy control subjects (Kerkhoff, 1999). Furthermore, Yelnik et al. (2002) showed that deviations of the SVV do not primarily depend on the localization and size of the underlying lesion, but are rather related to the presence and severity of spatial neglect. Thus, a severely disturbed representation of space in the frontal plane, or more general in all spatial planes, does not constitute an epiphenomenon, but rather a core deficit of neglect patients.

1.3. Rationale of the present project

A better understanding of the factors that mediate different aspects of spatial biases in visuospatial disorders and hemispatial neglect following (right) parietal brain lesions is important not only for obtaining a clearer picture of the nature and the underlying mechanisms of the spatial deficits but also for identifying potentially successful intervention schemes. Recent research revealed effective internal and external modulators of spatial deficits. Studies on the effectiveness of modulations of *internal* mediators of spatial deficits have used neck muscle vibration (e.g., Schindler et al., 2002), transcutaneous electroneural stimulation (TENS; Pizzamiglio et al., 1996), postural modulations (Karnath et al., 1998; Pizzamiglio et al., 1995), prism adaptation (e.g., Rossetti et al., 1998; Saevarsson et al., 2009; Vankilde & Habekost, 2010), and vestibular stimulation (Karnath, 1994); those on modulations of *external* (contextual) factors have employed optokinetic stimulation (e.g., Kerkhoff, 2000; Mattingley et al., 1994b) and cueing (e.g., Butter & Kirsch, 1995; Lin et al., 1996). This research enabled the development of the most applied neglect-therapies for spatially biased behaviour such as, for instance, extinction, the unawareness of contralesional stimuli, or motor neglect.

More recent research has focused on the subjective vertical as a direct measure of subjective space perception. A few studies investigating the effectiveness of internal mediators of space perception on the subjective vertical (SV) demonstrated that subjective verticality perception can be systematically modulated by changes in the setting of internal mediators contributing to the representation of space. Saj et al. (2005b, 2006, 2008) demonstrated that the visual SV in RBD patients (especially in neglect patients) was significantly affected by galvanic vestibular stimulation and by postural modulations (in the fore-back dimension). However, to our knowledge, no systematic investigation of the effects of *external / contextual* factors, which are known to critically influence other aspects of spatial behavior (Butter & Kirsch, 1995; Kerkhoff, 2000; Lin et al., 1996; Mattingley et al., 1994b), on SV judgments in RBD neglect has been carried out to date. Also, research investigating the effectiveness of therapeutic interventions for visuospatial disorders does not include reports on the effects of feedback-based orientation training on SV perception and orientation discrimination so far.

The present project aimed at conducting a comprehensive set of experiments in order to obtain a clearer picture of the nature and the underlying mechanisms of the spatial deficits in RBD neglect and to identify potential mediators of subjective space perception and potentially successful intervention schemes. Therefore, we investigated whether and how spatial orientation deficits in RBD neglect are modulated (1) by internal factors mediating the perception of verticality, including body posture and lateral head orientation, (2) by visual context as an external mediator of space perception and (3) by the systematic feedback-based training of visual line orientations.

1.3.1. Hypotheses

Visual, gravitational, and also other (e.g., somatosensory) information is integrated in the intraparietal cortex to generate a subjective percept of space (e.g., Bremmer et al., 2002; Duhamel et al., 1998). If information from different sources contributing to subjective space perception is congruent (that is, if the different frames of reference are aligned), the subjective perception of an orientation corresponds to the 'veridical' orientation. Even in healthy subjects without disturbed spatial information perception, the information delivered from different sources can be incongruent in certain conditions, as it is the case, for example, with a tilted head orientation, or a tilted visual context. Here, in addition to gravity, the tilted head or visual context serves as an additional frame of reference for the perception of the verticality and an orientation is consequently perceived with reference to head or frame orientation *and* to gravity, so that the resulting orientation judgment usually is a compromise between two or more references. By contrast, in neglect patients, the processing of gravitational input is impaired (i.e., asymmetric; e.g. Pizzamiglio et al., 1995) and gravitational information cannot be used as the predominant 'intrinsic' reference for the perception of the upright to the same extent as in healthy subjects. Therefore, it is suggested that RBD neglect patients show a pathological weighting of information integrated in parietal cortex to generate a subjective percept of space. With regard to manipulations of internal and external mediators of subjective space perception, they are assumed to display a much stronger impact of e.g. somatosensory or visual contextual information on subjective space perception.

Following this line of argumentation, we developed several hypotheses: (1) RBD neglect patients (but not brain-damaged control patients without neglect or healthy controls) generally exhibit a systematic visuospatial orientation deficit; that is, they generally display a substantial CCW tilt of their SV and other visual orientation judgements. (2) Axis orientation performance is differently modulated by internal (body posture, lateral head orientation) and external (visual context) modulators of subjective space perception in RBD neglect patients compared to control patients and healthy controls: SV judgements of all participants might generally vary as a consequence of the respective manipulation; however, performance of neglect patients should be *far more strongly* biased compared to all control groups, since these patients are assumed to be pathologically biased by internal and external cues as they cannot rely on gravitational information to the same extent as controls.

With regard to the effectiveness of feedback-based training of visual orientations, we did not have explicit hypotheses concerning the nature and extent of potential benefits. Some early clinical studies showed improvements of visuospatial performance with systematic training of perception in these patients (non-neglect RBD patients: e.g., Weinberg et al., 1982; Young et al., 1983; neglect RBD patients: e.g., Antonucci et al., 1995; Kerkhoff et al., 1998). For example, in a comprehensive rehabilitation study, Kerkhoff showed that visuospatial training has a positive effect on several measures of visuospatial and visuo-constructive performance in RBD patients with visuospatial and -constructive deficits and visual neglect (Kerkhoff, 1998). However, there are still only few effective therapeutic interventions for severe visuospatial disorders. In the present training study, we addressed the question whether (3) there is a beneficial effect of repetitive feedback-based visual orientation training on SV judgements and visual orientation discrimination. More precisely, we were interested in whether training effects are limited to the trained orientation or there is a transfer of training effects to other oblique orientations and to the SVV and SVH, transfer to other measures of visuospatial and -constructive performance, and interocular transfer. Finally we analyzed if a potential improvement persists over time and is equivalent in a follow-up test.

1.4. References

Andersen, R.A., Essick, G.K., & Siegel, R.M. (1985). The encoding of spatial location by posterior parietal neurones. *Science, 230,* 456-458.

Andersen, R.A., & Mountcastle, V.B. (1983). The influence of the angle of gaze upon the excitability of the light sensitive neurons of the posterior parietal cortex. *Journal of Neuroscience, 3,* 532-548.

Antonucci, G., Guariglia, C., Judica, A., Magnotti, L., Paolucci, S., Pizzamiglio, L., & Zoccolotti, P. (1995). Effectiveness of neglect rehabilitation in a randomized group study. *Journal of Clinical and Experimental Neuropsychology, 17,* 383-389.

Bender, M., & Jung, R. (1948). Abweichungen der subjektiven optischen Vertikalen und Horizontalen bei Gesunden und Hirnverletzten. *European Archives of Psychiatry and Clinical Neuroscience, 181,* 193-212.

Benton, A.L., Hannay, H.J., & Varney, N.R. (1975). Visual perception of line direction in patients with unilateral brain disease. *Neurology, 25,* 907-910.

Bisiach, E., Capitani, E., Luzatti, C., & Perani, D. (1981). Brain and conscious representation of outside reality. *Neuropsychologia, 19*, 543-551.

Bisiach, E., & Luzatti, C. (1978). Unilateral neglect of representational space. *Cortex, 14*, 129-133.

Bisiach, E., Pizzamiglio, L., Nico, D., & Antonucci, G. (1996). Beyond unilateral neglect. *Brain, 119*, 851-857

Brandt, Th., Dieterich, M., & Danek, A. (1994). Vestibular Cortex Lesions Affect the Perception of Verticality. *Annals of Neurology, 35*, 403-412.

Bremmer, F., Klam, F., Duhamel, J.-R., Ben Hamed, S., & Graf, W. (2002). Visual-vestibular interactive responses in the macaque ventral intraparietal area (VIP). *European Journal of Neuroscience, 16,* 1569-1586.

Brotchie, P.R., Andersen, R.A., Snyder, L.H., & Goodman, S.J. (1995). Head position signals used by parietal neurones to encode locations of visual stimuli. *Nature, 375,* 232-235.

Butter, C.M., & Kirsch, N. (1995). Effect of lateralized kinetic visual cues on visual search in patients with unilateral spatial neglect. *Journal of Clinical and Experimental Neuropsychology, 17,* 856-867.

Colby, C.L., & Duhamel, J.R. (1991). Heterogeneity of extrastriate visual areas and multiple parietal areas in the macaque monkey. *Neuropsychologia, 29(6),* 517-537.

Colby, C.L., & Goldberg, M. (1999). Space and attention in parietal cortex. *Annual Review of Neuroscience, 22,* 319-349.

Courtney, S.M., Ungerleider, L.G., Keil, K., & Haxby, J.V. (1996). Object and spatial visual working memory activate seperate neural systems in human cortex. *Cerebral Cortex, 6(1),* 39-49.

De Renzi, E., Faglioni, P., & Scotti, G. (1971). Judgment of spatial orientation in patients with focal brain damage. *Journal of neurology, neurosurgery, and psychiatry, 34*, 489-495.

De Renzi, E. (1982). *Disorders of space exploration and cognition.* Wiley, New York.

Desimone, R., & Ungedeider, L.G. (1989). Neural mechanisms of visual processing in monkeys. In F. Boller, & J. Grafman (Eds.), *Handbook of Neuropsychology, Vol.* 2. New York: Elsevier.

Duhamel, J.R., Colby, C.L., & Goldberg, M.E. (1998). Ventral intra-parietal area of the macaque: congruent visual and somatic response properties. *Journal of Neurophysiology, 79*, 126-136.

Eglin, M., Robertson, L.C., & Knight, R. T. (1989). Visual search performance in the neglect syndrome. *Journal of Cognitive Neuroscience, 1,* 372–385.

Faillenot, I., Sunaert, S., Van Hecke, P., & Orban, G. A. (2001). Orientation discrimination of objects and gratings compared: An fMRI study. *European Journal of Neuroscience*, *13*, 585–596.

Farah, M. J. (2004). *Visual Agnosia.* Cambridge, MA: MIT Press.

Ferber, S., & Karnath, H.O. (1999). Parietal and occipital lobe contributions to perception of straight ahead orientation. *Journal of neurology, neurosurgery, and psychiatry, 67*, 572-578.

Freedman, M., Leach, L., Kaplan, E., Shulman, K. I., & Delis, D. C. (1994). *Clock drawing: A neuropsychological analysis.* New York: Oxford University Press.

Gainotti, G., Tiacci, C. (1971). The relationships between disorders of visual perception and unilateral spatial neglect. *Neuropsychologia, 9(4),* 451-458.

Goodale, M.A., & Milner, A.D. (1992). Separate visual pathways for perception and action. *Trends in Neurosciences, 15(1),* 20-25.

Graziano, M.S.A., & Gross, C.G. (1995). The representation of extrapersonal space: A possible role for bimodal, visual-tactile neurons. In Gazzaniga, M.S. (Ed), *The Cognitive Neurosciences* (pp 1021-1034). Cambridge, MA: The MIT Press.

Grüsser, O.J., Pause, M., & Schreiter, U. (1990). Vestibular neurones in the parieto-insular cortex of monkeys (macaca fascicularis): visual and neck receptor responses. *Journal of Physiology, 430,* 559-583.

Halligan, P.W., & Marshall, J.C. (1991b). Spatial compression in visual neglect: a case study. *Cortex, 27*, 623-629.

Haxby, J.V., Grady, C.L., Horwitz, B., Ungerleider, L.G., Mishkin, M., Carson, R.E., & Herscovitch, P. (1991). Dissociation of object and spatial visual processing pathways in human extrastriate cortex. *Proceedings of the National Academy of Sciences of the United States of America, 88,* 1621-1625.

Hier, D.B., Mondlock, J., Caplan, L.R. (1983). Recovery of behavioral abnormalities after right hemisphere stroke. *Neurology, 33,* 345-350.

Howard, I.P. (1982). Human visual orientation. New York: Wiley.

Husain, M., & Nachev, P. (2007). Space and the parietal cortex. *Trends in Cognitive Science, 11(1),* 30-36.

Jesshope, H.J., Clark, M.S., Smith, D.S. (1991). The Rivermead Perceptual Assessment Battery: its application to stroke patients and relationship with function. *Clinical Rehabilitation, 5,* 115-122.

Kaplan, J., & Hier, D.B. (1982). Visuospatial deficits after right hemishpere stroke. *The American Journal of Occupational Therapy, 36(5),* 314-321.

Karnath, H.O. (1994). Subjective body orientation in neglect and the interactive contribution of neck muscle proprioceptive and vestibular stimulation. *Brain, 117,* 1001-1012.

Karnath, H.-O. (1997). Spatial orientation and the representation of space with parietal lobe lesions. *Philosophical Transactions of the Royal Society, London B, 352*, 1411 - 1419.

Karnath H.-O., Fetter M., & Niemeier M. (1998). Disentangling gravitational, environmental, and egocentric reference frames in spatial neglect. *Journal of Cognitive Neuroscience, 10*, 680–690.

Karnath, H.O., Ferber, S., & Himmelbach, M. (2001). Spatial awareness is a function of the temporal not the posterior parietal lobe. *Nature, 411,* 950-953.

Karnath, H.O., Fruhmann-Berger, M., Kuker, W., & Rorden, C. (2004). The anatomy of spatial neglect based on voxelwise statistical analysis: a study of 140 patients. *Cerebral Cortex, 14,* 1164-1172.

Karnath, H.O., & Rorden, C. (in press). The anatomy of spatial neglect. *Neuropsychologia*.

Kerkhoff, G. (1998). Rehabilitation of visuospatial cognition and visual exploration in neglect: a cross-over study. *Restorative Neurology & Neuroscience, 12,* 27-40.

Kerkhoff, G. (1999). Multimodal spatial orientation deficits in left-sided visual neglect. *Neuropsychologia, 37*, 1387-1405.

Kerkhoff, G. (2000). Multiple perceptual distortions and their modulation in patients with left visual neglect. *Neuropsychologia, 38(7),* 1073-86.

Kerkhoff, G. (2001). Spatial hemineglect in humans. *Progress in Neurobiology, 63,* 1-27.

Kerkhoff, G., & Zoelch, C. (1998). Disorders of visuo-spatial orientation in the frontal plane in patients with visual neglect following right or left parietal lesions. *Experimental Brain Research, 122*, 108-120.

Kim, Y., Morrow, L., Passafiume, D., & Boller, F. (1984). Visuoperceptual and visuomotor abilities an locus of lesion. *Neuropsychologia, 22(2),* 177-185.

Laplane, D., & Degos, J.D. (1983). Motor neglect. *Journal of Neurology, Neurosurgery, and Psychiatry, 46,* 152-158.

Lenz, H. (1944). Raumsinnesstörungen bei Hirnverletzungen. *Deutsche Zeitschrift für Nervenheilkunde, 157*, 22-64.

Lin, K.C., Cermak, S.A., Kinsbourne, M., & Trombly, C.A. (1996). Effects of left-sided movements on line bisection in unilateral neglect. *Journal of the International Neuropsychological Society, 2,* 404-411.

Mattingley, J.B., Bradshaw, J.L., Bradshaw, J.A. (1994). Horizontal visual motion modulates focal attention in left unilateral spatial neglect. *Journal of Neurology, Neurosurgery and Psychiatry, 57,* 1228-1235.

Maunsell, J.H.R., and Newsome, W.T. (1987). Visual processing in monkey extrastriate cortex. *Annual Review of Neuroscience, 10,* 363–401.

Meerwaldt, J.D., & Van Harskamp, F. (1982). Spatial disorientation in right-hemisphere infarction. *Journal of Neurology, Neurosurgery and Psychiatry, 45,* 586-590.

Mesulam, M.M. (1999). Spatial attention and neglect: parietal, frontal, and cingulate contributions to the mental representation and attentional targeting of salient extrapersonal events. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 354,* 1325-1346.

Milner, A.D., & Goodale, M.A. (1995). *The visual brain in action.* Oxford: Oxford University Press.

Milner, A.D., & Goodale, M.A. (2008). Two visual systems re-viewed. *Neuropsychologia, 46,* 774-785.

Milner, A.D., & Harvey, M. (1995). Distortion of size perception in visuospatial neglect. *Current Biology, 5,* 85-89.

Milner, A.D., Harvey, M., Roberts, R.C., & Forster, S.V. (1993). Line bisection errors in visual neglect: misguided action or size distortion? *Neuropsychologia, 31(1),* 39-49.

Mishkin, M., Ungerleider, L.G., & Macko, K.A. (1983). Object vision and spatial vision: two cortical pathways. *Trends in Neurosciences, 6,* 414-417.

Mort, D.J., Malhotra, P., Mannan, S.K., Rorden, C., Pambakian, A., Kennard, C., & Husain, M. (2003). The anatomy of visual neglect. *Brain, 126,* 1986-1997.

Newcombe, R., Ratcliff, G., & Damasio, H. (1987). Dissociable visual and spatial impairments following right posterior cerebral lesions: clinical, neuropsychological and anatomical evidence. *Neuropsychologia, 25(1b),* 149-161.

Newcombe, F. & Ratcliff, G. (1989). Disorders of visuo-spatial analysis. In F Boller, & J Grafman (Eds.), *Handbook of Neuropsychology*. New York: Elsevier.

Ng, V.W., Eslinger, P.J., Williams, S.C., Brammer, M.J., Bullmore, E.T., Andrew, C.M., Suckling, J., Morris, R.G., & Benton, A.L. (2000). Hemispheric preference in visuospatial processing: a complementary approach with fMRI and lesion studies. *Human brain mapping, 10(2),* 80-86.

Nichelli, P., Rinaldi, M., & Cubelli, R. (1989). Selective spatial attention and length representation in normal subjects and in patients with unilateral spatial neglect. *Brain and cognition, 9(1),* 57-70.

Pérennou, D. (2006). Postural disorders and spatial neglect in stroke patients: A strong association. *Restorative Neurology and Neuroscience, 24(4-6),* 319-334.

Pérennou, D., Mazibrada, G., Chauvineau, V., Greenwood, R., Rothwell, J., Gresty, M.A., & Bronstein, A.M. (2008). Lateropulsion, pushing and verticality perception in hemispheric stroke: a causal relationship? *Brain, 131,* 2401-2413.

Perenin, M.T. (1997). Optic ataxia and unilateral neglect: clinical evidence for dissociable spatial functions in posterior parietal cortex. In H.O. Karnath, & P. Thier (Eds.), *Parietal lobe contributions to orientation in 3D space.* Berlin: Springer.

Pizzamiglio, L., Vallar, G., & Doricchi, F. (1995). Gravity and hemineglect. *NeuroReport, 7*, 370 –371.

Pizzamiglio, L., Vallar, G., & Magnotti, L. (1996). Transcutaneous electrical-stimulation of the neck muscles and hemineglect rehabilitation. *Restorative Neurology and Neuroscience, 10,* 197-203.

Pohl, W. (1973). Dissociation of spatial discrimination deficits following frontal and parietal lesions in monkeys. *Journal of Comparative and Physiological Psychology, 82(2),* 227-239.

Riddoch, M.J., Humphreys, G.W., Jacobson, S., Pluck, G., Bateman, A., & Edwards, M. (2004). Impaired orientation discrimination and localisation following parietal damage: on the interplay between dorsal and ventral processes in visual perception. *Cognitive Neuropsychology, 21(6),* 597-623.

Rizolatti, G., & Matelli, M. (2003). Two different streams form the dorsal visual system: anatomy and functions. *Experimental Brain Research, 153,* 146-157.

Rossetti, Y., Rode, G., Pisella, L., Farné, A., Boisson, D., & Perenin, M.T. (1998). Prism adaptation to a rightward optical deviation rehabilitates left hemispatial neglect. *Nature, 98,* 166-169.

Sack, A.T., Hubl, D., Prvulovic, D., Formisano, E., Jandl, M., Zanella, F.E., Maurer, K., Goebel, R., Dierks, T., & Linden, D.E.J. (2001). The experimental combination of rTMS and fMRI reveals the functional relevance of parietal cortex for visuospatial functions. *Cognitive Brain Research, 13,* 85-93.

Saevarsson, S., Kristjánsson, Á., Hildebrandt, H., & Halsband, U. (2009). Prism adaptation improves visual search in hemispatial neglect. *Neuropsychologia, 47(3),* 717-725.

Saj, A., Honoré, J., Davroux, J., Coello, Y., & Rousseaux, M. (2005). Effect of posture on the perception of verticality in neglect patients. *Stroke, 36*, 2203-2205.

Saj, A., Honoré, J., & Rousseaux, M. (2006). Perception of the vertical in patients with right hemispheric lesion: Effect of galvanic vestibular stimulation. *Neuropsychologia, 44,* 1509-1512.

Saj, A., Honoré, J., Bernati, T., Richard, C., & Rousseaux, M. (2008). Reducing rightward bias of subjective straight ahead in neglect patients by changes in body orientation. *Journal of Neurology, Neurosurgery, and Psychiatry, 79(9),* 991-996.

Sakata, H., Taira, M., Kusunoki, M., Murata, A., & Tanaka, Y. (1997). The parietal association cortex in depth perception and visual control of hand action. *Trends in Neuroscience, 20*, 350-357.

Sakata, H., Taira, M., Kusunoki, M., Murata, A., Tanaka, Y., & Tsutsui, K. (1999). Neural coding of 3D features of objects for hand action in the parietal cortex of the monkey. In G. W. Humphreys, J. Duncan, & A. Treisman (Eds.), *Attention, space and action.* Oxford: Oxford University Press.

Schindler, I., Kerkhoff, G., Karnath, H.O., Keller, I., & Goldenberg, G. (2002). Neck muscle vibration induces lasting recovery in spatial neglect. *Journal of Neurology, Neurosurgery & Psychiatry, 73,* 412-419.

Shikata, E., Hamzei, F., Glauche, V., Koch, M., Weiller, C., Binkofski, F., et al. (2003). Functional properties and interactions of the anterior and posterior intraparietal areas in humans. *European Journal of Neuroscience*, *17*, 1105–1110.

Snyder, L.H., Batista, A.P., & Andersen, R.A. (1997). Coding of intention in the posterior parietal cortex. *Nature, 386,* 167.

Taira, M., Kawashima, R., Inoue, K, & Fukada, H. (1998). A PET study of axis orientation discrimination. *Neuroreport, 9(2),* 283-288.

Tartaglione, A., Benton, A.L., Cocito, L., Bino, G., & Favale, E. (1981). Point localization in patients with unilateral brain damage. *Journal of Neurology, Neurosurgery and Psychiatry, 44,* 935-941.

Tartaglione, A., Cocito, L., Bino, G., Pizio, N., & Favale, E. (1983). Further evidence for asymmetry of point localization in normals and unilateral brain damaged patients. *Neuropsychologia, 21,* 407-412.

Taylor, A.M., & Warrington, E.K. (1973). Visual discrimination in patients with localized cerebral lesions. *Cortex, 9,* 82-84.

Tranel, D., Vianna, E., Manzel, K., Damasio, H. & Grabowski, T. (2009). Neuroanatomical correlates of the Benton Facial Recognition Test and Judgement of Line Orientation Test. *Journal of Clinical and Experimental Neuropsychology, 31(2),* 219-233.

Ungerleider, L.G., & Haxby, J.V. (1994). ‚What‘ and ‚where‘ in the human brain. *Current Opinion in Neurobiology, 4(2),* 157-165.

Ungerleider, L.G., & Mishkin, M. (1982). Two cortical visual systems. In D.J. Ingle, R.J.W. Mansfield, & M.S. Goodale (Eds.), The Analysis of Visual Behavior. Cambridge, MA: MIT Press.

Ungerleider, L.G., Courtney, S.M., & Haxby, J.V. (1998). A neural system for human visual working memory. *Proceedings of the National Academy of Sciences of the United States of America, 95,* 883-890.

Utz, K.S., Keller, I., Artinger, F., Stumpf, O., Funk, J., & Kerkhoff, G. (2011). Multimodal and multispatial deficits of verticality perception in hemispatial neglect. *Neuroscience, 188*, 68-79.

Vaina, L.M., Lemay, M., Bienfang, D.C., Choi, A.Y. & Nakayama, K. (1990). Intact "biological motion" and "structure from motion" perception in a patient with impaired motion mechanisms: a case study. *Visual Neuroscience, 5,* 353–369.

Vallar, G., & Perani, D. (1986). The anatomy of unilateral neglect after right hemisphere stroke lesions. A clinical/CT-scan correlation study in man. *Neuropsychologia, 24,* 609-622.

Vandenberghe, R., Dupont, P., De Bruyn, B., Bormans, G., Michiels, J., Mortelmans, L., & Orban, G.A. (1996). The influence of stimulus location on the brain activation pattern in detection and orientation discrimination. A PET study of visual attention. *Brain, 119,* 1263-1276.

Vangkilde, S., & Habekost, T. (2010). Finding Wally: Prism adaptation improves visual search in chronic neglect. *Neuropsychologia, 48(7),* 1994-2004.

Verdon, V., Schwartz, S., Lovblad, K.O., Hauert, C.A., & Vuilleumier, P. (2010). Neuroanatomy of hemispatial neglect and ist functional components: a study using voxel-based lesion-symptom mapping. *Brain, 133,* 880-894.

Von Cramon, D., & Kerkhoff, G. (1993). On the cerebral organization of elementary spatial perception. In B. Gulyas, D. Ottoson, & P. Roland (Eds.), *Functional oranisation of the human visual cortex.* Oxford: Pergamon.

Warrington, E.K., & James, M. (1967). Disorders of visual perception in patients with localised cerebral lesions. *Neuropsychologia, 5,* 253-266.

Weinberg, J., Piasetsky, E., Diller, L., & Gordon, W. (1982). Treating perceptual organization deficits in nonneglecting RBD stroke patients. *Journal of Clinical and Experimental Neuropsychology, 4,* 59-74.

Yelnik, A. P., Lebreton, F. O., Bonan, I. V., Colle, F., Meurin, F. A., Guichard, J. P., & Vicaut, E. (2002). Perception of Verticality After Recent Cerebral Hemispheric Stroke. *Stroke*, *33*, 2247-2253.

Young, G.C., Collins, D., & Hren, M. (1983). Effect of pairing scanning training with block design training in the remediation of perceptual problems in left hemiplegics. *Journal of Clinical Neuropsychology, 5,* 201-212.

Zihl, J., von Cramon, D., Mai, N. & Schmid, C. (1991). Distrubance of movement vision after bilateral posterior brain damage. Further evidence and follow up observations. *Brain 114,* 2235–2252.

Chapter 2: Studies on individual research questions

2.1. Systematic biases in the tactile perception of the subjective vertical in patients with unilateral neglect and the influence of upright vs. supine posture

Funk, J., Finke, K., Mueller, H.J., Preger, R., & Kerkhoff, G. (2010a).

Neuropsychologia, 48(1), 298-308.

2.1.1. Abstract

Patients with right hemisphere lesions often show contralesional neglect. Recent research focused on deficits beyond the typical neglect symptoms observed in the horizontal plane. Studies investigating deficits in the frontal and sagittal plane revealed impairments in the judgment of the subjective vertical. Systematic deviations in the subjective vertical have been demonstrated in the visual and tactile modality, indicating a supramodal spatial orientation deficit. Further, the magnitude of deviations appears to be manipulable by modulations of body posture. The present study investigated the subjective *tactile* vertical (STV) in neglect patients in the frontal and sagittal plane and its dependence on posture. Neglect patients and healthy controls performed tactile-spatial judgments of axis orientations in supine and upright posture. Neglect patients displayed a marked variability as well as a systematic tilt in their STV judgments. The STV was tilted counterclockwise in the frontal and backward in the sagittal plane. This tilt was larger in severe compared to moderate neglect patients, while it was not evident in healthy subjects. Our results support previous evidence and indicate a multisensory spatial orientation deficit in neglect patients which is related to neglect severity. Further, we found that performance of neglect patients deteriorated in supine compared to upright posture. This finding conflicts with the suggestion of a performance benefit in supine posture due to reduced (asymmetric) gravitational input. The negative effect of supine posture on the spatial bias in neglect is discussed with respect to a presumably further reduced intrinsic alertness state in the typically hypo-aroused neglect patients.

Keywords: Hemineglect; Space perception; Subjective vertical; Tactile; Posture; Alertness

2.1.2. Introduction

Neglect is a supramodal neurological disorder characterized by a complex syndrome of sensory, motor and representational deficits (for a review, see Kerkhoff, 2001). Patients with hemispatial neglect fail to detect or respond to stimuli in their contralesional hemispace (Bisiach, Pizzamiglio, Nico, & Antonucci, 1996), show unilateral spatial representational deficits (Bisiach & Luzatti, 1978; Bisiach, Capitani, Luzatti, & Perani, 1981) and frequently display a reduced use of their contralesional extremities (Laplane & Degos, 1983). By definition, for diagnosing neglect, these deficits must not be primarily due to sensory, motor or cognitive/emotional impairments. Neglect frequently occurs after infarctions in the territory of the right (less often of the left) middle cerebral artery (Vallar, 1993), causing lesions which center on the inferior parietal cortex (BA 40, 7; Mort et al., 2003; but see Karnath, Ferber, & Himmelbach, 2001, for a different view).

Different mechanisms have been suggested as the underlying cause of the syndrome. These include deficits in the spatial allocation of attention to the left hemifield (e.g., Desimone & Duncan, 1995; Heilman & Watson, 1977; Kinsbourne, 1987; 1993; Mesulam, 1998) that result in either lateralized orienting (Làdavas, Petrino, & Umiltà, 1990) or biased attentional weighting (Duncan et al., 1999); deficits in the transformation of sensory information into motor action (e.g. Jeannerod & Biguer, 1987; Karnath, 1997; Vallar, 1997); a disturbed mental representation of space, i.e., especially of contralesional information (e.g. Bisiach & Luzatti, 1978; Bisiach et al., 1996; Milner, 1987; Halligan & Marshall, 1991); and/or spatially non-lateralized impairments of attentional capacity, i.e., deficits in visuo-spatial working memory (Husain, Mannan, Hodgson, Wojciulik, Driver, & Kennard, 2001) and in vigilance/sustained attention (Robertson & Manly, 1999) that affect information processing in both hemifields.

All of these current models of neglect focus on the explanation of deficits in the horizontal plane. Such deficits are apparent, for example, as left-sided omissions in visual search, reading, writing and drawing tasks, as deficits in (horizontal) size perception in the contralesional hemispace (Milner & Harvey, 1995; Milner, Harvey, Roberts, & Forster, 1993), as a compression of contralesional hemispace (Gainotti & Tiacci, 1971; Nichelli, Rinaldi, & Cubelli, 1989) or even both hemispaces (Halligan & Marshall, 1991), as rightward deviations in line bisection and in pointing straight ahead, and as a deviation of space representation toward the ipsilesional hemispace (Karnath, 1997).

However, numerous studies have demonstrated deficits in visuospatial perception and visuomotor performance in patients with right-sided parietal lesions that cannot result solely from impairments restricted to the horizontal plane (for a review, see De Renzi, 1982). These include impairments in visual orientation discrimination and position estimation (Warrington & James 1967; Taylor & Warrington 1973; Tartaglione, Benton, Cocito, Bino, & Favale, 1981; Tartaglione, Cocito, Bino, Pizio, & Favale, 1983) as well as deficits in the judgment of the subjective visual vertical (SVV) and horizontal (SVH; Howard, 1982; Lenz 1944; De Renzi, Faglioni, & Scotti, 1971), and judgments of oblique line orientations (Kim, Morrow, Passafiume, & Boller, 1984; Benton, Hannay, & Varney, 1975). Such deficits in the judgment of the principal axes represent abnormalities in visuospatial perception in another spatial plane: the frontal (or roll) plane (see figure 1).

Interestingly the lesions leading to impairments in the frontal plane and in the horizontal plane involve the human homologue of the monkey parieto-insular-vestibular cortex (Brandt, Dieterich, & Danek, 1994), the posterior insula, postcentral gyrus, and the supramarginal gyrus (Cramon & Kerkhoff, 1993) and, thus, are neighboring those lesions causing neglect behavior. Accordingly, Kerkhoff and Zoelch (1998) found that 12 out of 13 neglect patients showed deficits in visuospatial judgments of axis orientation in the vertical, horizontal and oblique orientation. The deficits were not a general consequence of brain damage because patients with left or right hemisphere lesions, but without neglect, performed at the level of healthy control subjects. Furthermore, Yelnik and colleagues (2002) showed that deviations of the SVV do not primarily depend on the localization and size of the underlying lesion, but are rather correlated with the severity of spatial neglect. In summary, these findings indicate a severe disturbance in the representation of space in the frontal plane in neglect patients which is related to the severity of neglect and, thus, does not seem to constitute an epiphenomenon, but rather one of the core deficits of these patients.

Comparably to impairments in the horizontal plane, those in the roll plane seem to be multimodal (or even supramodal). De Renzi, Faglioni, and Scotti (1971) found that patients with right posterior lesions are significantly impaired in both the visual and the tactile perception of the horizontal and the vertical axis. Kerkhoff (1999) additionally showed that counter-clockwise tilts of the main visual and tactile spatial axes were associated with each other and that tilts in both modalities were correlated with the severity of the clinical neglect. CCW tilts observed in a crossmodal axis orientation test (Kerkhoff, 1999) support the assumption of a supramodal spatial orientation deficit. In a recent large-scale study with 80 stroke patients, Pérennou et al. (2008) found that patients with right hemisphere lesions showed visual (in 55% of the subjects), tactile (32.5%) and postural tilts (42%) to the contralesional side in the frontal plane. Right parietal lesions caused the most marked supramodal (visual and tactile) tilts in the frontal plane, which led the authors to conclude that the right cerebral hemisphere is crucially involved in the elaboration of an internal model for verticality perception.

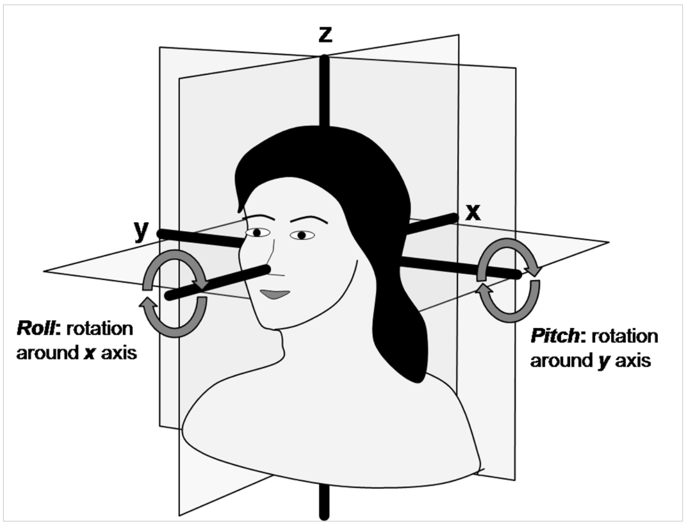

Figure 1: Schematic illustration of the three orthogonal planes defining three-dimensional space: frontal or roll plane, sagittal or pitch plane and horizontal or yaw plane.

Saj, Honoré, Bernati, Coello, and Rousseaux (2005) extended the assessment of spatial representations into a third, the sagittal (or pitch) plane (see figure 1). Neglect patients were presented with a luminous bar which they had to rotate and orient in a vertical position, either in the roll plane or in the pitch plane. The CCW tilt of the SVV in the roll plane was replicated. Furthermore, in the sagittal plane, too, neglect patients showed a systematic deviation from the true vertical, that is, a significant *backward* tilt of the SVV (hence towards the observer).

A further experiment of the Kerkhoff (1999) study was the first to demonstrate influences of body posture, specifically, lateral head inclination, on visual and tactile orientation judgments in a neglect patient (but not in a healthy control subject). The orientation deficits of the patient were significantly aggravated by a tilt of the head to the left by 25°, and significantly reduced by a comparable rightward tilt. This finding suggests that deficits in spatial orientation judgments are significantly modulated by gravitational input in neglect patients.

In a follow-up study, Saj, Honoré, Davroux, Coello, and Rousseaux (2005b) systematically investigated the effects of body posture and gravitational information on the perception of the visuohaptic subjective vertical in the roll plane. Neglect patients and healthy control subjects oriented a bar into a subjectively vertical position in four different body posture conditions: (1) sitting with plantar sole support, (2) sitting without plantar sole support, (3) sitting with legs extended on a support, and (4) supine body position. It is important to note that the *graviceptive* information was varied via the modulation of the otholitic input only in the supine body position. In all other postures, only the *somatosensory* information changed, but the graviceptive input was kept stable. It was found that the body posture had a significant effect on SVV judgments in the neglect patients, but not in the control subjects. The CCW tilts of neglect patients decreased from position (1) through positions (2) and (3) to position (4), whereby the supine body position differed significantly from the three sitting positions. These data indicate that the progressive change of body posture and the accompanying modulation of graviceptive input and somatosensory afferences resulted in a progressive reduction of the bias in the subjective perception of verticality in neglect patients. Positive effects of lying body position on line bisection deviations (Pizzamiglio, Vallar, & Doricchi, 1995) and of a backward-tilted body position on exploration bias (Karnath, Fetter, and Niemeier, 1998) have also been documented in neglect.

In summary these findings indicate that the integration of sensory (retinal, proprioceptive, and vestibular) input is perturbed in patients with hemispatial neglect, leading to an asymmetrical processing of incoming information which contributes to the distortion of spatial representations. This interpretation is supported by the observation that stimulation of vestibular, proprioceptive, and visual sources contributing to spatial representations can influence symptoms of spatial hemineglect (for reviews, see Kerkhoff, 2001; Vallar, 1997). Regarding vestibular information processing, graviceptive input from the left and right otholitic system is not processed symmetrically after unilateral cerebral lesions affecting or disrupting neural circuitry critical for the processing of graviceptive information (e.g.

Pizzamiglio et al., 1995). In supine position, the influence of otholitic input on judgments of orientations in space is reduced due to a decreasing sensitivity of the utricles with increasing backward tilt of the head, leading to deteriorations of orientation judgments (Howard, 1982). In patients with spatial neglect, a reduction of the influence of pathologically disturbed graviceptive input in the lying body position might therefore reduce the (in this case disrupting) effect of graviceptive information on the perception and representation of space (Pizzamiglio et al., 1995; Saj et al., 2005b; Saj et al., 2008).

The supramodal spatial perception and representation impairments of neglect patients do not only affect the horizontal, but also other spatial planes (e.g., Kerkhoff & Zoelch, 1998; Saj et al., 2005a). Although different potential mechanisms might underlie deviations of the subjective vertical in these planes, the tilts in all planes can be interpreted as manifestations of a *generally* deficient representation of spatial information. The severity and variability of the tilts of the principal axes were shown to correlate with that of spatial neglect in both the visual and the tactile modality (Kerkhoff, 1999). For the SVV (Saj et al., 2005b), it has been furthermore documented that the deviations are influenced by body posture.

To our knowledge, however, the effect of posture has not been systematically studied on the subjective *tactile* vertical (STV) in the frontal and sagittal plane. Thus, the aim of the present investigation was to close the gap between recent studies on the subjective vertical in neglect patients (Kerkhoff, 1999; Kerkhoff & Zoelch, 1998; Saj et al., 2005a; 2005b) by examining the STV in the frontal (roll) and sagittal (pitch) plane dependent on body position in patients with right hemisphere damage and spatial neglect. By blindfolding subjects to exclude the visual modality, we selectively investigated the influence of vestibular and proprioceptive input on verticality judgments. In line with previous findings (Kerkhoff, 1999; Saj et al., 2005b), we assumed that patients with spatial neglect would show a systematic CCW tilt of the STV in the roll plane and a systematic backward tilt of the STV in the pitch plane. In an upright body posture, we expected vestibular input to play a dominant role in verticality perception, whereas in the lying body posture, the impact of vestibular input was expected to be reduced and that of somatosensory input to be decisive (e.g., Anastasopoulos, Bronstein, Haslwanter, Fetter, &, Dichgans, 1999; Howard, 1982). Since the processing of vestibular information is deficient in patients with spatial neglect (e.g., Lafosse, Kerckhofs, Troch, Santens, & Vandenbussche, 2004; Pérennou, 2006; Pizzamiglio et al., 1995), the systematic tilt of the STV was expected to be reduced in lying compared to upright body posture. From these considerations, we derived the following hypotheses: (1) Neglect patients show larger STV deviations than healthy control subjects. (2) The neglect patients' tilt is systematic: it is CCW in the frontal plane and backwards in the sagittal plane. (3) Neglect patients show reduced STV tilts in the lying compared to an upright body posture. (4) There is a significant positive correlation between the severity of neglect and the size and variability of the STV tilt.

2.1.3. Methods

Subjects

20 patients with right hemispheric vascular lesions and left spatial neglect and 20 healthy control subjects participated in the experiment. Informed consent according to the Declaration of Helsinki II was obtained from all subjects. Table 1 summarizes the demographic and clinical data. Gender differences between the neglect patients and the healthy controls were assessed via the coefficient of contingency 'chi'. The number of male to female participants was not significantly different in the two groups ($\chi^2 = 0.40$, $P > 0.50$). All participants were right-handed. None of the patients suffered from hemiplegia or hemiparesis of the right upper limb. All of the patients had experienced a relatively recent hemorrhagic (subarachnoid or intracerebral) or ischemic stroke. Time since lesion varied between 1-8 months (mean = 2.5

months, S.D. = 1.7 months). The age of the neglect patients ranged from 33 to 78 years, mean age was 57 years (S.D. = 12.0 years). The healthy control group consisted of ten subjects who were age-matched to the neglect patients (31-73 years; mean = 56.1 years; S.D. = 12.9 years) and ten younger subjects (age 20-29; mean = 25.4 years; S.D. = 3.1 years). To check for possible confounds due to age effects in the healthy control subjects, separate ANOVAs with the factors group (young vs. old control), plane (roll, pitch) and posture (supine, upright), were calculated for each of the STV parameters preceding the analysis of interest. Since these ANOVAs did not reveal a significant effect of age or any interaction with other factors, healthy control subjects (age-matched and younger controls) were combined in one control group for further analyses.

Neglect tests

All patients underwent detailed screening for visual neglect, including four well-established neglect screening tests: paper-and-pencil horizontal line bisection, the star cancellation and the letter cancellation subtests of the behavioral inattention battery (BIT; Wilson, Cockburn, & Halligan, 1987), and a neglect-sensitive reading test of 49-52 words. Cutoffs were deviations of more than 5 mm from the true midpoint of a 20 cm line in line bisection, more than 4 omissions in the star cancellation and in the letter cancellation tasks, and more than two omissions or substitutions of letters or words and/or prolonged reading times (> 40 sec). A neglect severity index was computed as the sum of the tests with values above the cut-off. The neglect indices as well as the performance in the four screenings are listed in table 1 for each subject group and for patients individually. Patients showed systematic deficits typical for spatial neglect: a shift of the subjective midpoint to the right in line bisection, high omission rates (especially in the left hemispace) in cancellation tasks, and impaired reading performance.

Table 1: Summary of clinical and demographic data of the neglect patients (single subject data and group mean) and healthy controls (group mean).

Subject	Sex	Age Years	Etiology	Lesion side, localization	TSL (months)	Hemi-plegia	Line bisection	Stars L / R	E&R L / R	Reading errors	Neglect -Index
C old	**5M/5F**	**56.1**	-	-	-	-	**-1.5**	**0.1 / 0.5**	**0.2 / 1.2**	**0.4**	**0**
C young	**5M/5F**	**25.4**	-	-	-	-	**1.6**	**0.3 / 0.1**	**0.4 / 0.5**	**0.4**	**0**
N1	M	57	Infarct	right: fronto-temporal, basal ganglia	1	-	-3	0 / 0	0 / 0	0	0
N2	F	52	ICB	right: temporo-parietal, basal ganglia	2	-	+2	0 / 0	0 / 0	0	0
N3	M	56	ICB	right: basal ganglia	4	+	+12	2 / 1	3 / 0	0	1
N4	M	66	Infarct	right: basal ganglia	2	+	+3	0 / 1	5 / 0	1	1
N5	F	61	ICB	right: basal ganglia	1.5	-	+5	1 / 0	2 / 0	0	1
N6	M	56	Infarct	right: fronto-temporal	2	+	+2	7 / 5	1 / 3	0	1
N7	M	70	Infarct	right: fronto-parieto-occipital	2.5	+	0	1 / 0	2 / 0	2	1
N8	M	33	ICB	right: frontal	1.5	+	-10	0 / 0	3 / 4	1	2
N9	M	61	Infarct	right: fronto-temporo-parietal, basal ganglia; left: temporo-parietal	2.5	+	+7	0 / 1	1 / 7	0	2
N10	F	43	Infarct	right: temporo-parieto-occipital	8	+	-22	0 / 0	3 / 0	5	2
N11	F	71	Infarct	right: temporo-parietal	1	+	+1	2 / 2	3 / 4	10	3
N12	M	54	Infarct	right: temporal, thalamus	5	+	-13	0 / 5	1 / 1	4	3
N13	M	61	SAB	right: basal ganglia	1.5	+	+13	0 / 3	4 / 1	13	3
N14	M	58	ICB	right: temporo-parietal, thalamus	3	+	+23	3 / 3	0 / 5	15	4
N15	F	42	Infarct	right: temporo-parietal	2.5	+	+7	16 / 0	10 / 3	4	4
N16	F	49	Infarct	right: fronto-temporo-parietal	3	+	-59	23 / 18	20 / 18	40	4
N17	F	58	ICB	right: basal ganglia	3	+	+22	8 / 5	2 / 7	11	4
N18	M	38	Infarct	right: temporo-parietal	1	+	+17	21 / 8	15 / 8	17	4
N19	F	76	Infarct	right: occipital; bilateral: thalamus, basal ganglia	1	+	+40	7 / 3	8 / 4	5	4
N20	M	78	ICB	right: fronto-temporo-parietal	2	+	+52	27 / 18	20 / 14	40	4
N mean	**12M/8F**	**57**	-	-	**2.5**	**17**	**+5**	**5.9 / 3.7**	**5.2 / 4**	**8.4**	**2.4**

Abbreviations: C: healthy control subject; N: neglect patient; m: male; f: female; ICH: intracerebral hemorrhage; SAH: subarachnoid hemorrhage; TSL: time since lesion; Hemiparesis: + means hemiparesis present, **-** means hemiparesis absent; line bisection: **-** means deviation to the left, + means deviation to the right; stars: star cancellation; E&R: letter cancellation, L: left, R: right; Neglect-Index: index of severity of neglect symptoms (summed score of four neglect screening tests).

Tactile-spatial tests

The subjective tactile vertical (STV) was measured in an angle-fitting procedure in two spatial planes (frontal and sagittal) and two body postures (upright and supine). Subjects were presented with two metal rods (length: 15 cm, width: 4 mm) attached to a plate (height: 50 cm, width: 40 cm). The plate contained two rods (an upper and a lower one) in order to allow subjects to accomplish the task using the rod which was easier to reach for them. The experimental plate was mounted on a bench (34 cm high) vertically 0.5 m in front of the patient. The plate could be rotated on the bench in the horizontal plane, which permitted the STV in the participants' frontal and sagittal plane to be tested. The rod was rotatable on a semi-circle in the plate plane. Along the radius of the rotatable rod, a scale comprising 180° (horizontal left: 0°, vertical: 90°, horizontal right: 180°) allowed for the measurement of the angle of the rod in steps of 1° (see figure 2).

Following the neglect screening, the experimental setup (height of the plate, height and distance of the chinrest to the plate) was adjusted to the individual participant and calibrated with the aid of a plumb-line to the earth vertical. In the upright posture condition, the head and body of the subject was oriented earth-vertical, with subjects being seated on an experimental chair with a supporting head- and chinrest. Subjects were seated in front of a desk on which the experimental plate on the bench was mounted. In the supine position condition, participants were lying on a medical stretcher adjustable in height and positioned in a near earth-horizontal position. Trunk and head were slightly elevated, approximately 10° from the horizontal. Head position was stabilized by two pillows. The left arm was positioned along the left thigh in all subjects and stabilized with a scarf in patients with hemiplegia. At the start of each condition, participants were familiarized with the material and the task and subsequently blindfolded with an eye mask to exclude the influence of visual information. Moreover, to avoid horizontal or vertical reference cues, participants were not allowed to tactilely explore the whole experimental setup, especially the angles of the plate and the bench. In each condition, the apparatus was centered relative to the mid-sagittal plane of the participant, and the distance between the participant and the rod (0.5 m) was kept similar.

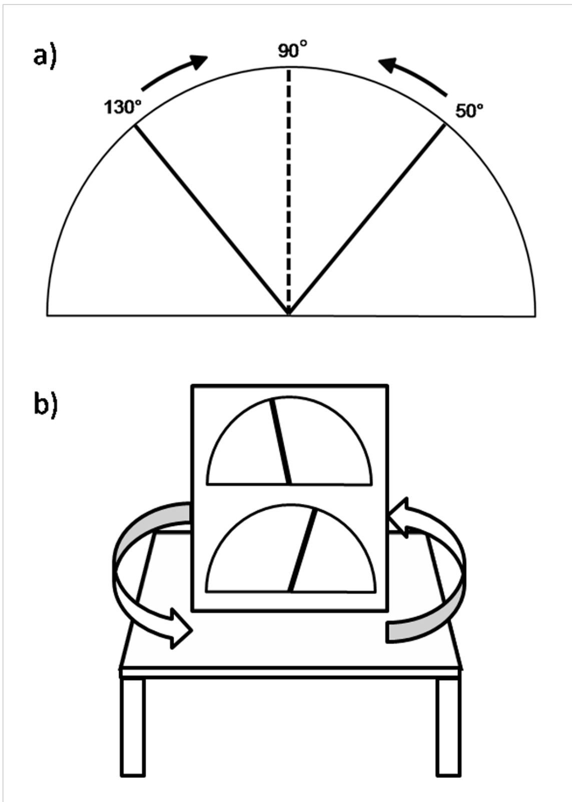

Figure 2: Experimental setup. 1a) Subjects adjusted a rod to their STV, starting at 50° or 130°. 1b) The setup contained two rods (an upper and a lower one) and subjects accomplished the task using the rod that was easier to reach for them. The rods were attached to a plate which was mounted on a bench and could be rotated on the bench in the transverse plane, permitting testing in the frontal and sagittal plane.

Participants' task was to adjust the metal rod to their STV with their right, dominant, hand. Each participant accomplished four blocked experimental conditions: STV in the sagittal and frontal plane, in upright and supine body posture. To avoid sequence or practice effects, the sequence of the conditions was counterbalanced across subjects. Each subject received two practice trials prior to testing in each condition. Subjects performed 10 trials per condition with balanced starting positions, that is, each five trials starting 40° clockwise (CW) or, respectively, counter-clockwise (CCW) from the true vertical. Between blocks, participants had the opportunity to take a short break. Time for STV adjustment was not limited, in order to enable patients to compensate for any motor or attention deficits. STV angles in degrees were registered by the experimenter on a protocol sheet.

2.1.4. Results

Subjective tactile vertical - parameters

As a measure of the central tendency of STV deviation from the true vertical, constant errors were computed: individual STV adjustments were subtracted from 90° and averaged across all trials within a condition. This parameter displays possible systematic CW or CCW tendencies of the STV in each experimental condition (CW deviations: negative sign; CCW deviations: positive sign). Additionally, mean error size (=unsigned errors) was computed as a measure of the amplitude of the deviation. Mean error size was calculated via the absolute values of the deviations, thus disregarding their directions. Furthermore, the interval of uncertainty was determined, in terms of the complete range within which the subject considered the displayed rod as being exactly vertical (biggest – smallest STV value).

Condition sequence and starting position

In a first step, to control for possible confounds, effects of starting position and condition sequence were assessed in separate ANOVAs with the factors group (neglect, control), plane (roll, pitch) and posture (supine, upright), i.e. two ANOVAs (one including the factor condition sequence and one the factor starting position) were calculated for each STV parameter. Significant interactions with the possible confounding variable were followed-up by further ANOVAs and post-hoc comparisons.

Neither the sequence of the conditions nor the starting position did have an effect on any STV parameter (all $P > 0.10$). There were no significant interactions between condition sequence or starting position and any other factor ($P > 0.10$), except one: for the intervals of uncertainty, there was a significant four-way interaction between plane, posture, group and starting position ($F(1, 38) = 5.49$; $P < 0.05$). This interaction was based on larger intervals of uncertainty of neglect patients in the pitch plane when the starting position was directed towards the subject, especially in the upright posture. Interestingly, in the roll plane, starting position did not have an effect on STV parameters, neither did it interact with the factor subject group, i.e. the direction of movement did not influence the performance of neglect patients. Since the observed interaction is not related in any way to our hypothesis on effects and interactions between the factors of interest, starting position and condition sequence were not included in the further analysis of the data.

Size of deviations

According to our hypotheses, neglect patients were expected to display larger deviations of the STV compared to healthy control subjects. Furthermore, the size of deviations in the neglect patients was suggested to be sensitive to posture manipulations. To assess the size of STV deviations, the mean unsigned errors and intervals of uncertainty were determined. Figures 3 and 4 display the intervals of uncertainty and the mean unsigned errors of the two groups for both postures in the roll and the pitch plane. As can be seen, in both planes and for both postures, intervals of uncertainty and mean unsigned errors were larger in the neglect patients compared to healthy control subjects.

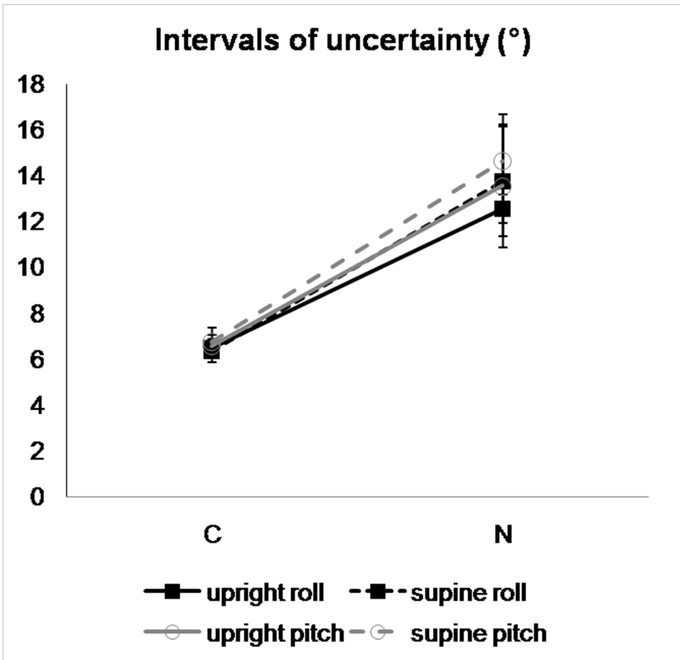

Figure 3: Mean intervals of uncertainty (and associated SEM) of neglect patients and healthy controls for both body postures in the roll and pitch plane. C, healthy control subjects; N, patients with neglect; performance in the roll plane is shown in black, performance in the pitch plane is shown in grey; solid lines indicate performance in upright posture, dashed lines indicate performance in supine posture.

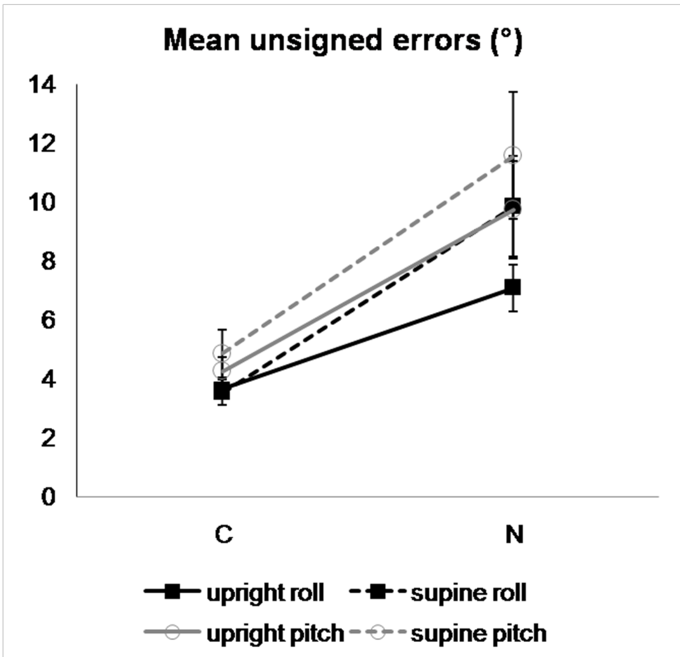

Figure 4: Mean unsigned errors (and associated SEM) of neglect patients and healthy controls for both body postures in the roll and pitch plane. C, healthy control subjects; N, neglect patients; performance in the roll plane is shown in black, performance in the pitch plane is shown in grey; solid lines indicate performance in upright posture, dashed lines indicate performance in supine posture.

Separate mixed (2x2x2) ANOVAs with the factors group (neglect, control), plane (roll, pitch) and posture (supine, upright) were calculated for mean unsigned errors and intervals of uncertainty. ANOVAs revealed a significant 'group' effect on the intervals of uncertainty [$F(1, 38) = 11.37$; $P < 0.01$] and on the mean error size [$F(1, 38) = 13.15$; $P < 0.01$], i.e. neglect patients showed significantly larger intervals of uncertainty and mean unsigned errors in their STV judgments than healthy controls. For the intervals of uncertainty, there was no further main effect ($P > .30$) or significant interaction ($P > .30$). However, for the mean unsigned errors, there was a significant main effect of plane [$F(1, 38) = 8.20$; $P < 0.01$], a significant main effect of posture [$F(1, 38) = 5.53$; $P < 0.05$] and a by trend significant interaction between group and posture [$F(2, 38) = 3.63$; $P < 0.07$]. In general, subjects showed significantly larger unsigned errors in the pitch plane compared to the roll plane and in supine compared to upright posture. The difference between posture conditions was more pronounced in the neglect patients compared to healthy controls, i.e. neglect patients performed significantly worse in supine compared to upright posture [$t(19) = 2.36$; $P < 0.05$], while healthy controls did not show such a significant difference ($P > 0.60$).

Direction of tilt

According to our second hypothesis, the tilt of the STV was expected to be systematic in neglect patients (but not in healthy control subjects) such that the tilt would be CCW in the frontal plane, and backwards in the sagittal plane. The constant errors were determined to depict the direction of STV deviations. Figure 5 presents the mean values (and associated standard errors) of the parameter constant errors for both subject groups in both posture conditions in the roll and pitch plane. As can be seen, constant errors were larger (more positive) in the neglect group compared to the healthy control subjects in both the roll and pitch plane and for both posture conditions.

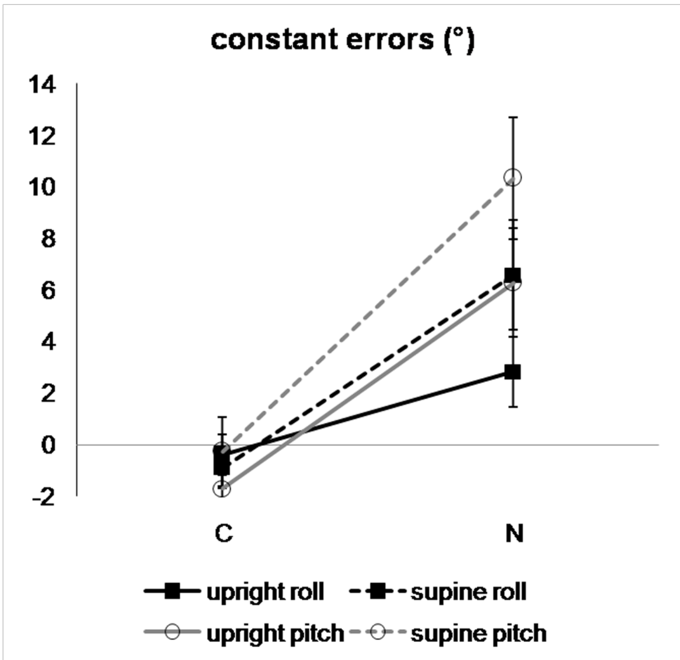

Figure 5: Mean constant errors (and associated SEM) of neglect patients and healthy controls for both body postures in the roll and pitch plane. C, healthy control subjects; N, neglect patients; performance in the roll plane is shown in black, performance in the pitch plane is shown in grey; solid lines indicate performance in upright posture, dashed lines indicate performance in supine posture.

As for the other STV parameters, a 2x2x2 ANOVA with the factors group (neglect, control), plane (roll, pitch) and posture (supine, upright) was calculated for the constant errors. The ANOVA revealed a significant 'group' effect [F(1, 38 = 14.75; P < 0.01], i.e. neglect patients showed significantly larger (more positive) constant errors than healthy controls. There was a trend towards significance for the factor plane [F(1, 38) = 3.74; P = 0.06] and a significant effect of posture [F(1, 38) = 15.35; P < 0.01]. Across all subjects, constant errors were larger in the pitch plane compared to the roll plane and in supine compared to upright posture. Furthermore, there was a significant interaction between the factors group and plane [F(1, 38) = 5.56; P < 0.05] and group and posture [F(1, 38) = 9.51; P < 0.01] indicating that effects of both plane and posture were more pronounced in neglect patients, i.e. patients displayed significantly worse performance in the pitch compared to the roll [t(19) = 2.59; P < 0.05] and in supine compared to upright posture [t(19) = 4.30; P < 0.01], while healthy controls did not show such effects (all P > 0.45). Figure 6 illustrates the constant errors individually for each subject in both planes (across postures). As can be seen, constant errors of healthy subjects do not differ systematically from zero into any direction, whereas constant errors of most neglect patients differ systematically from zero in a positive direction, with larger deviations in the severe neglect patients. Additional one sample t-tests comparing the constant errors of each group to zero deviation (i.e. the objective vertical) were calculated to demonstrate that differences in constant errors between neglect patients and healthy controls were due to significant CCW deviations of neglect patients' subjective verticals. T-tests showed that constant errors of healthy subjects did not differ significantly from zero [$t(19) = -0.93$; $P > 0.35$]. By contrast, constant errors of neglect patients revealed a significant positive deviation from zero indicating a CCW tilt of their STV judgments [$t(19) = 3.95$; $P < 0.01$].

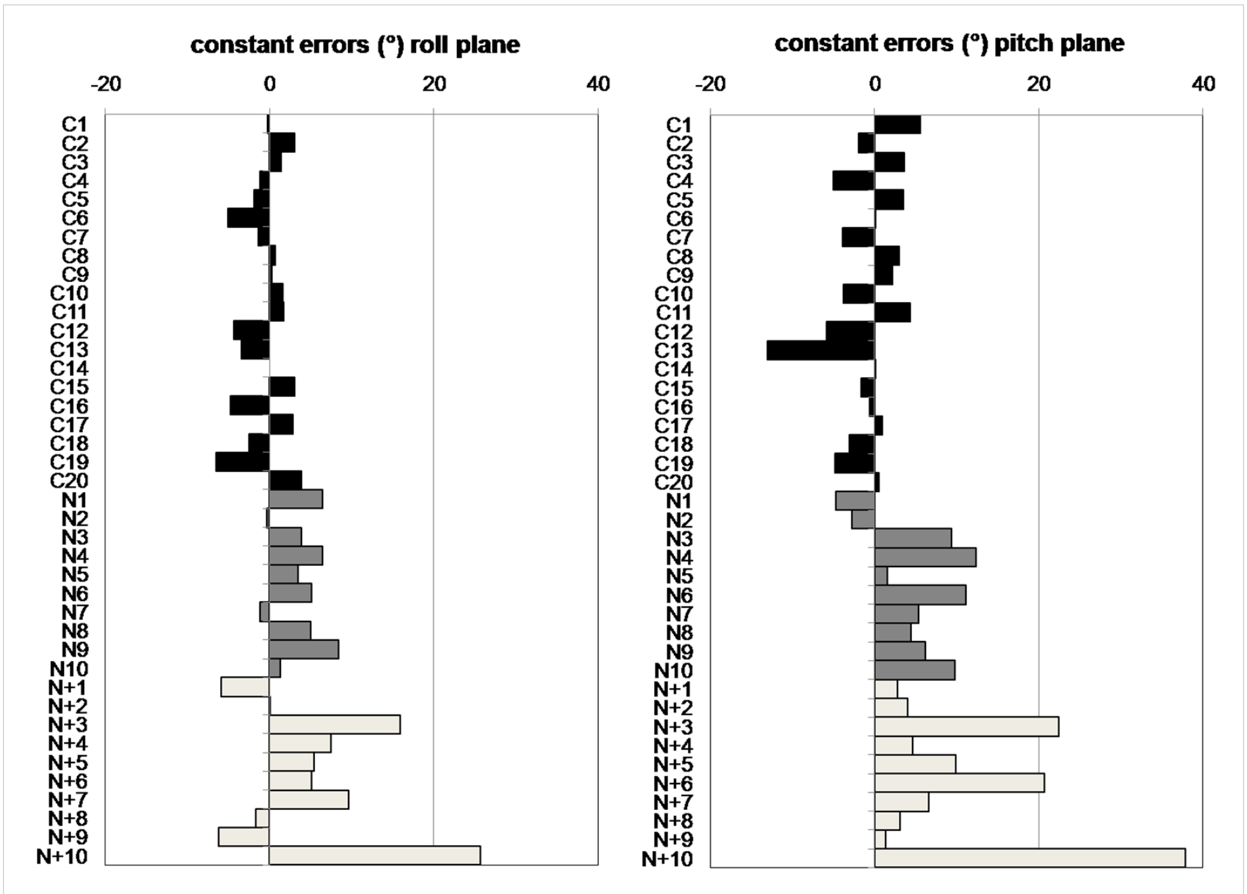

Figure 6: Constant errors of individual participants in the roll and pitch plane (averaged across postures). C = healthy control subject; N = moderate neglect (neglect index ≤ 2); N+ = severe neglect (neglect index ≥ 3); in the patients, neglect indices increase from top to bottom.

Relation between neglect severity and STV

Hypothesis 4 predicted a relationship between the severity of the neglect and the size of the STV deviations. To evaluate whether the tactile-spatial deficits observed in our study were related to neglect, we correlated the individual STV parameters of each neglect patient (constant errors, mean unsigned errors and intervals of uncertainty averaged across postures and planes) with the composite neglect severity score. Spearman rank correlations revealed no significant correlation with neglect severity for the constant errors ($r = 0.21$; $P > 0.15$) and the mean unsigned errors ($r = 0.21$; $P > 0.15$). The correlation between the interval of uncertainty and the neglect severity index tended to be significant ($r = 0.33$; $P < 0.09$). To further analyze the relation between typical neglect performance in individual screening tests and performance in our tactile-spatial task, we computed Pearson correlations between the STV parameters of the neglect patients (constant errors, mean unsigned errors and intervals of uncertainty averaged across postures and planes) and the patients' performance in the individual screening tests (line bisection, star cancellation, E&R cancellation and reading). Table 2 displays the Pearson correlation coefficients. As can be seen all three STV parameters were significantly correlated with performance in both cancellation tasks whereas line bisection performance was correlated only with constant errors and reading performance was not correlated with any parameter.

	Star cancellation	E&R cancellation	Line bisection	Reading errors
Intervals of uncertainty	0.67**	0.63**	0.19	0.42
Unsigned errors	0.61**	0.59**	0.42	0.21
Constant errors	0.57**	0.53*	0.54*	-0.07

Table 2: Pearson correlations between the STV parameters of the neglect patients (constant errors, mean unsigned errors and intervals of uncertainty averaged across postures and planes) and the patients' performance in the individual screening tests (line bisection, star cancellation, E&R cancellation and reading). ** $P < 0.01$ (2-tailed); * $P < 0.05$ (2-tailed).

Further, to compare performance of all subjects in the roll and the pitch plane, Pearson correlations were computed to assess correlations between STV parameters in the two planes, i.e. each parameter in the roll plane (averaged across posture conditions) was correlated with the same parameter in the pitch plane. Correlations between STV parameters in the roll and pitch plane were highly significant (all $r > 0.75$; all $P < 0.01$) indicating that subjects showed highly comparable patterns of results in the two planes.

2.1.5. Discussion

Recently, deficits beyond the horizontal plane have been described in neglect patients that include impairments also in the frontal (roll) and the sagittal (pitch) plane (e.g., Saj et al., 2005; Kerkhoff & Zoelch, 1998; Kerkhoff, 1999). CCW deviations of the SVV and STV in the roll plane and backwards directed deviations of the SVV in the pitch plane (Kerkhoff & Zoelch, 1998; Kerkhoff, 1999; Saj et al., 2005a) were shown to be related to neglect severity (Kerkhoff & Zoelch, 1998; Kerkhoff, 1999). Further, Saj et al. (2005b) found that SVV deviations were modulated by the patients' body posture.

The aim of the present study was to investigate the subjective tactile vertical (STV) in neglect patients in the roll and the pitch plane dependent on the body posture (which had not been examined thus far). Our hypotheses stated that: (1) neglect patients would show larger STV deviations than controls; (2) STV tilts would be systematic in neglect patients: in the frontal plane the STV is tilted CCW, in the sagittal plane it is tilted backwards; (3) neglect patients would show reduced STV tilts in supine compared to upright posture; and (4) the size of STV deviations would be related to the severity of neglect.

Support for a multimodal spatial orientation deficit in neglect

The first and second hypotheses were clearly supported by our data: Neglect patients displayed a marked variability (larger intervals of uncertainty) and increased mean error amplitude (larger unsigned errors) as well as a systematic tilt (positive constant errors) in their STV judgments. Neglect patients' STV judgments varied within a wider range than those of healthy controls, and the ranges and mean error amplitudes tended to be larger for patients with severe compared to those with moderate neglect. Also, the patients took substantially longer to make their STV judgments. This pattern mirrors neglect patients' uncertainty regarding the judgment of verticality and more generally spatial orientation.

Neuropsychological studies investigating the neural basis of the subjective vertical in the visual domain implicate cortical contributions from the posterior insula (Brandt et al., 1994), the parieto-insular-vestibular cortex (Grüsser et al., 1990), and the postcentral and supramarginal gyri (Cramon & Kerkhoff, 1993) as well as subcortical contributions from thalamic, especially paramedian (Dieterich & Brandt, 1993) and brainstem (Friedmann, 1970) areas for processing of axis orientation. Based on this evidence, Brandt and colleagues (1994) suggested that deviations of the subjective vertical are related to lesions in any brain structure in a graviceptive pathway, extending from the brainstem through the posterior thalamus to the vestibular cortex. Recently, Perennou et al. (2008) showed that the most marked *supramodal* (visual and tactile) tilts in the frontal plane were associated with right parietal lesions, which led the authors to conclude that the right cerebral hemisphere (especially the right parietal lobe) is crucially involved in the elaboration of an internal model for verticality perception.

The patients examined in the present study had contracted lesions of structures that might be involved in a neural network underlying the representation of space. Lesion sites included the temporoparietal cortex, the thalamus, and the basal ganglia, which all are involved in neural circuits connecting the thalamus with cortical structures.

Besides larger STV ranges, the neglect patients displayed systematic CCW tilts in the roll plane and even larger backward tilts in the pitch plane. Healthy subjects, by contrast, did not exhibit systematic STV tilts. Patients with severe neglect tended to display larger systematic tilts than patients with moderate neglect. CCW tilts of the STV in neglect patients have already been found by Kerkhoff (1999), and backward tilts of the SVV in the pitch plane have been demonstrated by Saj and colleagues (2005a). However, our data for the first time reveal backward tilts of the subjective *tactile* vertical in the pitch plane in neglect patients. We found that not only in the frontal, but also in the sagittal plane, neglect patients show systematic tilts of the subjective *tactile* vertical in the same direction as their subjective *visual* vertical. This finding of identical tilts in the visual and tactile modalities supports the assumption of a multisensory or even supramodal spatial orientation deficit in neglect patients (Kerkhoff, 1999), suggesting that damage to certain, multimodal neurons is responsible for the deficits in the perception and representation of the principal spatial axes (that become manifest in identical tilts in different modalities). According to the recent findings by Pérennou et al. (2008), the anatomical substrate of this supramodal or transmodal tilt (in their terminology) is found in the right parietal cortex. This suggests that the right parietal cortex is involved in the elaboration of an internal model of verticality, as well as in the distribution of spatial attention towards the contralesional hemispace; that is, the same brain region is involved in the processing of spatial information in different spatial planes.

Based on single-cell recordings in monkey parietal cortex, Sakata and colleagues (1997) have identified a class of so-called 'axis-orientation-selective' neurons in the lateral bank of the caudal part of the intraparietal sulcus, which are relevant for the coding of axis orientation in three-dimensional space. Since bimodal neurons have been described in the monkey putamen and parietal areas (Graziano & Gross, 1995; Duhamel, Colby, & Goldberg, 1998), such neurons might also be activated by the touch of objects with similar spatial orientations.

Moreover, cells in the posterior parietal cortex have been reported to contribute to the representation of space by integrating multimodal afferent (and reafferent) information via 'gain-field modulation' (Andersen, Essick, & Siegel, 1985). For instance, parietal areas 7a and LIP (lateral intraparietal) receive visual signals as well as eye position signals, with cells' receptive fields being modulated by eye position (Andersen & Mountcastle, 1983; Andersen et al., 1985). Approximately half of these cells also have gain fields for the head, including efference copies of motor signals, but also vestibular signals and neck proprioceptive signals (Brotchie et al., 1995; Snyder et al., 1997), to account for head movements in space. This is in line with the view that systematic tilts of the coordinate systems can be caused not only by lesions of the parietal cortex, but also by damage to other parts of a complex system underlying the representation of space, including lesions of the central vestibular pathways (brain stem, thalamus, or vestibular cortex), as well as sensory pathways and regions involved in visuospatial disturbances such as (right) parietal lesions.

Effect of posture on STV tilt

Following unilateral cerebral lesions affecting neural circuitry critical for the processing of graviceptive information, input from the left and right otholitic system is no longer processed symmetrically (e.g., Pizzamiglio et al., 1995). Reductions of the influence of otholitic input in a lying body position (e.g., Howard, 1982) would therefore reduce the (in this case biased) effect of graviceptive information on the representation of space. Saj and colleagues (2005b) showed that CCW tilts of the SVV after right hemisphere lesions decreased from an upright to a supine posture, indicating that the change of body posture and the accompanying modulation of graviceptive input results in a reduction of the bias in the subjective vertical. Our third hypothesis was that such reductions of spatial bias demonstrated in the visual domain would also be found in the *tactile* domain, resulting in reduced STV tilts in supine compared to upright posture. However, the comparisons between intervals of uncertainty, mean error size and constant errors of neglect patients in supine and upright posture did *not* reveal improved performance (i.e., reduced STV tilts) in the supine position. On the contrary, neglect patients showed significantly *larger* constant errors and unsigned errors in the *supine* compared to upright posture. This pattern of results is at variance with our expectation of a reduced bias in a lying position. It seems to be in direct opposition to the findings of Saj and colleagues (2005b), and also in conflict with several other studies which have documented similar effects of head and body position on performance in visual-spatial tasks in neglect patients (e.g., Pizzamiglio et al., 1995; Karnath et al., 1998).

One explanation for this inconsistence might be that the effect of posture on tilts of the subjective vertical is based on differential mechanisms in the visual and tactile domains. However, our finding that the subjective *tactile* vertical is tilted in the same direction as the subjective *visual* vertical (as documented in comparable studies of the SVV) does not support this view. Furthermore, Kerkhoff (1999) demonstrated that tilts of the subjective vertical do not only occur in a unimodal, but also a crossmodal task, indicative of a supramodal/central deficit in the representation of space underlying tilts of the subjective vertical.

Given this, the question arises whether there were decisive methodological differences between our study and the previous study of Saj et al. (2005b). In the study of Saj and colleagues (2005b), patients had to complete only 6 trials per body position. Further, the authors note that "task completion was fast, whatever the group" (p. 2204), indicating that patients spent only little time in supine posture during their experiment. In contrast, in the present study, patients spent one experimental session (i.e., at least half an hour) in lying body position and completed 24 trials (2 practice trials and 10 valid trials for each plane) with breaks in-between. Although none of the subjects fell asleep during the experimental sessions, it is likely that the alertness/vigilance of the patients was decreased in the lying body position.

Consistent with this, we observed signs of fatigue in most patients already after a few minutes in supine position. Interestingly, research on the effects of postural changes on levels of arousal and awareness in vegetative and minimally conscious state patients (Elliott et al., 2005) indicates that positional changes have a significant impact on alertness, arousal, and behavior in such patients. It is plausible that this effect – at least to some extent – also applies to patients with milder reductions of alertness and vigilance. Therefore, neglect patients, too, might respond to postural changes with changes in alertness and performance.

There is converging evidence that biases in spatial attention and processing of spatial information is significantly influenced by levels of alertness. Several studies in healthy subjects showed that reductions in alertness can induce neglect-like symptoms (Manly et al., 2005; Fimm et al., 2006; Matthias et al., 2009). Further, it has been shown that the right hemisphere is not only involved in regulating spatial attention, but also alertness and vigilance (Sturm & Willmes, 2001). Parietal and frontal structures of the right hemisphere underlying the regulation of vigilance and spatial orientation are largely overlapping (Sturm et al., 1999) indicating direct links between (intrinsic and phasic) alertness and spatial attention.

This link between alertness and spatial bias is especially critical in neglect patients who suffer from a combination of a spatial-attentional asymmetry and a reduced level of (intrinsic) alertness. In patients with visual hemineglect, the strongest rightward biases can be observed in subjects whose intrinsic alertness state is especially low (Bartolomeo & Chokron, 2002; Cramon & Kerkhoff, 1993; Heilman, Watson, & Valenstein, 1993). Conversely, phasically alerting neglect patients temporarily reduces their rightward bias (Robertson et al., 1996), and increasing intrinsic alertness leads to reductions of spatial hemineglect symptoms associated with increased activity in frontal and parietal brain regions of the right hemisphere (Thimm et al., 2006; Sturm et al., 2006; see also Robertson et al., 1995).

We assume that the alertness of neglect patients was reduced in supine position in the present study. This change in alertness in turn might have influenced the magnitude of the spatial bias displayed by our patients. Since neglect patients typically suffer from hypo-arousal already, minor fluctuations in alertness which are not effective in healthy subjects yet, might suffice to increase their spatial biases. Thus, the larger spatial biases in lying body position (in the form of increased STV parameters constant errors) may well have been due to further reduced alertness in supine position. At first sight, this line of argumentation conflicts with the assumption of a reduced spatial bias in supine posture due to an attenuated impact of graviceptive information. However, our data do not necessarily contradict the reasoning underlying this assumption. In fact, such a mechanism could have been effective in the present study as well, but masked by the effect of reduced alertness on the spatial bias. On the other hand, in the study of Saj and colleagues (2005b), there may not (yet) have been a modulation (or there may have been only a minor modulation) of alertness in supine position, so that the effect of the reduced impact of graviceptive input in supine posture on the spatial bias in neglect patients was not masked by variations in alertness. Thus, the findings of the two studies are not mutually exclusive; rather, they might reflect different combinations of mechanisms underlying the performance of patients in the respective experimental setup.

Correlation with neglect severity

Several studies have shown that the degree to which the subjective vertical in neglect patients deviates from the objective vertical is correlated to neglect severity (Kerkhoff & Zoelch, 1998; Kerkhoff, 1999; Yelnik et al., 2002). We did not find statistically significant correlations between the neglect indices and STV parameters in our patients. However, neglect indices were, by trend, correlated with intervals of uncertainty, indicating that general neglect severity influences the variability of spatial judgments. Furthermore, inspection of the distribution of single subject STV parameters (see e.g. figure 6) indicates systematically larger parameters in the patients with severe compared to moderate neglect. Thus, there appears to be a relation between neglect severity and tactile spatial performance. However, the imprecise nature of the neglect indices (i.e. number of tests with an 'impaired' score, instead of the accurate degree of impairment in each of them) and/or the large standard deviations of STV parameters in the patient groups might have decreased the probability of finding significant correlations. Thus, we calculated additional correlations between patients' performance in individual screening tests and the STV parameters. All STV parameters were highly correlated with patients' performance in the two cancellation tasks. These data are in close agreement with previous data showing a close association between deficits in the tactile vertical (in the roll plane) and visual neglect (Kerkhoff, 1999). Line bisection performance was correlated significantly with the constant errors which represent the systematic tilt of the subjective vertical, but only marginally to the magnitude of deviations (unsigned errors and intervals of uncertainty). There is evidence that cancellation tests have greater test-retest reliability and are often more sensitive for detecting neglect than e.g. line bisection test (Kinsella, Packer, Ng, Olver, & Stark; Marsh & Kersel, 1993) which might explain why correlations with line bisection performance are not as high. Reading performance was only poorly correlated to the magnitude of STV deviation, but not the systematic bias.

In summary, our results support earlier findings by Kerkhoff (1999) indicating a close relation between deficits in the subjective tactile vertical and neglect symptoms. However, the strength of correlations between tactile-spatial performance and neglect performance seems to vary in different tests.

Conclusion

In conclusion, the results of the present study can be taken as evidence for a (multimodal) spatial orientation deficit in neglect patients, which is evident in multiple spatial planes (roll and pitch) and can be modulated by posture. However, to fully account for effects of posture on the spatial bias of neglect patients, it is necessary to incorporate various aspects and implications of postural change. Our results indicate that not only modulations of the impact of gravitational input, but also variations in alertness might affect spatial information processing.

Acknowledgements

This work was supported by a Deutsche Forschungsgemeinschaft (DFG) grant to Peter Bublak, Kathrin Finke, and Georg Kerkhoff (project FOR 480, BU 1327/2-1)

2.1.6. References:

Anastasopoulos, D., Bronstein, A., Haslwanter, T., Fetter, M., &, Dichgans, J. (1999). The role of somatosensory input for the perception of verticality. *Annals of the New York Academy of Sciences*, *871,* 379-383.

Andersen, R.A., Essick, G.K., & Siegel, R.M. (1985). The encoding of spatial location by posterior parietal neurones. *Science, 230,* 456-458.

Andersen, R.A., & Mountcastle, V.B. (1983). The influence of the angle of gaze upon the excitability of the light sensitive neurons of the posterior parietal cortex. *Journal of Neuroscience, 3,* 532-548.

Bartolomeo, P., & Chokron, S. (2002). Orienting of attention in left unilateral neglect. *Neuroscience and Biobehavioral Reviews, 26*(2), 217-234.

Benton, A., Hannay, H.J., & Varney, N.R. (1975). Visual perception of line direction in patients with unilateral brain disease. *Neurology, 25,* 907-910.

Bisiach, E., Capitani, E., Luzatti, C., & Perani, D. (1981). Brain and conscious representation of outside reality. *Neuropsychologia, 19*, 543-551.

Bisiach, E., & Luzatti, C. (1978). Unilateral neglect of representational space. *Cortex, 14*, 129-133.

Bisiach, E., Pizzamiglio, L., Nico, D., & Antonucci, G. (1996). Beyond unilateral neglect. *Brain, 119*, 851-857.

Brandt, Th., Dieterich, M., & Danek, A. (1994). Vestibular Cortex Lesions Affect the Perception of Verticality. *Annals of Neurology, 35*, 403-412.

Brotchie, P.R., Andersen, R.A., Snyder, L.H., & Goodman, S.J. (1995). Head position signals used by parietal neurones to encode locations of visual stimuli. *Nature, 375,* 232-235.

Cramon, D. von, & Kerkhoff, G. (1993). On the cerebral organization of elementary visuo-spatial perception. In B. Gulays, D. Ottoson, P. Roland (Eds), *Functional organisation of the human visual cortex* (pp 211-231). Oxford: Pergamon.

De Renzi, E. (1982). *Disorders of space exploration and cognition.* Wiley, New York.

De Renzi, E., Faglioni, P., & Scotti, G. (1971). Judgment of spatial orientation in patients with focal brain damage. *Journal of neurology, neurosurgery, and psychiatry, 34*, 489-495.

Desimone, R., & Duncan, J. (1995). Neural mechanisms of selective visual attention. *Annual Review of Neuroscience, 18,* 193-222.

Dieterich, M., & Brandt, T. (1993). Thalamic infarctions: differential effects on vestibular function in the roll plane. *Neurology, 43, 1*732-1740.

Duhamel, J.R., Colby, C.L., & Goldberg, M.E. (1998). Ventral intra-parietal area of the macaque: congruent visual and somatic response properties. *Journal of Neurophysiology, 79*, 126-136.

Duncan, J., Bundesen, C., Olson, A., Humphreys, G., Chavda, S., & Shibuya, H. (1999). Systematic analysis of deficits in visual attention. *Journal of Experimental Psychology, General, 128*, 450-478.

Elliott, L., Coleman, M., Shiel, A., Wilson, B.A., Badwan, D., Menon, D., & Pickard, J. (2005). Effect of posture on levels of arousal and awareness in vegetative and minimally conscious state patients: a preliminary investigation. *Journal of Neurology, Neurosurgery, and Psychiatry, 76,* 298-299.

Fimm, B., Willmes, K., & Spijkers, W. (2006). The effect of low arousal on visuo-spatial attention. *Neuropsychologia, 44*, 1261-1268.

Friedmann, G. (1970). The judgment of the visual vertical and horizontal with peripheral and central vestibular lesions. *Brain, 93,* 313-328.

Gainotti, G., Tiacci, C. (1971). The relationships between disorders of visual perception and unilateral spatial neglect. *Neuropsychologia, 9(4),* 451-458.

Graziano, M.S.A., & Gross, C.G. (1995). The representation of extrapersonal space: A possible role for bimodal, visual-tactile neurons. In Gazzaniga, M.S. (Ed), *The Cognitive Neurosciences* (pp 1021-1034). Cambridge, MA: The MIT Press.

Grüsser, O.J., Pause, M., & Schreiter, U. (1990). Vestibular neurones in the parieto-insular cortex of monkeys (macaca fascicularis): visual and neck receptor responses. *Journal of Physiology, 430,* 559-583.

Halligan, P.W., & Marshall, J.C. (1991b). Spatial compression in visual neglect: a case study. *Cortex, 27*, 623-629.

Heilman, K.M., & Watson, R.T. (1977). The neglect syndrome – a unilateral defect of the orienting response. In S. Harnad, R.W. Doty, L. Goldstein, J. Jaynes, G. Krauthamer (Eds.), Lateralization in the nervous system. New York: Academic Press.

Heilman, K. M., Watson, R. T., & Valenstein, E. (1993). Neglect and related disorders. In K. M. Heilman & E. Valenstein (Eds.), *Clinical Neuropsychology* (pp. 279–336). Oxford: Oxford University Press.

Howard, I.P. (1982). Human visual orientation. New York: Wiley.

Husain, M., Mannan, S., Hodgson, T., Wojciulik, E., Driver, J., & Kennard, C. (2001). Impaired spatial working memory across saccades contributes to abnormal search in parietal neglect. *Brain, 124(5),* 941-952.

Jeannerod, M., & Biguer, B. (1987). The directional coding of reaching movements. A visuomotor conception of spatial neglect. In M. Jeannerod (Ed.), Neurophysiological and Neuropsychological Aspects of Spatial Neglect (S87-113). Amsterdam: North Holland.

Karnath, H.-O. (1997). Spatial orientation and the representation of space with parietal lobe lesions. *Philosophical Transactions of the Royal Society, London B, 352*, 1411 - 1419.

Karnath, H.-O., Ferber, S., & Himmelbach, M. (2001). Spatial awareness is a temporal not a posterior parietal lobe function. *Nature, 411*, 950-953.

Karnath H.-O., Fetter M., & Niemeier M. (1998). Disentangling gravitational, environmental, and egocentric reference frames in spatial neglect. *Journal of Cognitive Neuroscience, 10*, 680–690.

Kerkhoff, G. (1999). Multimodal spatial orientation deficits in left-sided visual neglect. *Neuropsychologia, 37*, 1387-1405.

Kerkhoff, G. (2001). Spatial hemineglect in humans. Progress in Neurobiology, 63, 1-27.

Kerkhoff, G., & Zoelch, C. (1998). Disorders of visuo-spatial orientation in the frontal plane in patients with visual neglect following right or left parietal lesions. *Experimental Brain Research, 122*, 108-120.

Kim, Y., Morrow, L., Passafiume, D., & Boller, F. (1984). Visuoperceptual and visuomotor abilities an locus of lesion. *Neuropsychologia, 22,* 177-185.

Kinsbourne, M. (1987). Mechanisms of unilateral neglect. In M. Jeannerod (Ed.), Neurophysiological and Neuropsychological Aspects of Spatial Neglect (S. 69-86). Amsterdam: North-Holland.

Kinsbourne, M. (1993). Orientational bias model of unilateral neglect: evidence from attentional gradients within hemispace. In I.H. Robertson, J. Marshall (Eds.), Unilateral Neglect: Clinical and Experimental Studies (S. 63-86). Hove: LEA publishers.

Kinsella, G., Packer, S., Ng, K., Olver, J., & Stark, R. (1995). Continuing issues in the assessment of neglect. *Neuropsychological Rehabilitation, 5,* 239-258.

Làdavas, E., Petronio, A., & Umiltà, C. (1990). The deployment of visual attention in the intact field of hemineglect patients. *Cortex, 26(3),* 307-317.

Lafosse, C., Kerckhofs, E., Troch, M., Santens, P., & Vandenbussche, E. (2004). Graviceptive misperception of the postural vertical after right hemispheric damage. *Neuroreport, 15(5),* 887-891.

Laplane, D., & Degos, J.D. (1983). Motor neglect. *Journal of Neurology, Neurosurgery, and Psychiatry, 46,* 152-158.

Lenz, H. (1944). Raumsinnesstörungen bei Hirnverletzungen. *Deutsche Zeitschrift für Nervenheilkunde, 157*, 22-64.

Manly, T., Dobler, V. B., Dodds, C. M., & George, M. A. (2005). Rightward shift in spatial awareness with declining alertness. *Neuropsychologia, 43*, 1721-1728.

Marsh, N.V., & Kersel, D.A. (1993). Screening tests for visual neglect following stroke. *Neuropsychological Rehabilitation, 3,* 245-257.

Matthias, E., Bublak, P., Müller, H. J., Schneider, W. X., Krummenacher, J. & Finke, K. (2009). The influence of alertness on spatial and non-spatial components of visual attention. *Journal of Experimental Psychology: Human Perception and Performanc.* (in press).

Mesulam, M.M. (1985). Principles of Behavioral Neurology. Philadelphia: F.A. Davis; 1985.

Mesulam, M.M. (1998). From sensation to cognition. *Brain, 121*, 1013-1052.

Milner, A.D. (1987). Animal models for the syndrome of spatial neglect. In M. Jeannerod (Ed.), Neurophysiological and Neuropsychological Aspects of Spatial Neglect (S. 259-288). Amsterdam: North-Holland.

Milner, A.D., & Harvey, M. (1995). Distortion of size perception in visuospatial neglect. *Current Biology, 5*, 85-89.

Milner, A.D., Harvey, M., Roberts, R.C., & Forster, S.V. (1993). Line bisection errors in visual neglect: misguided action or size distortion? *Neuropsychologia, 31(1),* 39-49.

Mort, D.C., Malhotra, P., Mannan, S.K., Rorden, C., Pambakian, A., Kennard, C., & Husain, M. (2003). The anatomy of visual neglect. *Brain, 126*, 1986-1997.

Nichelli, P., Rinaldi, M., & Cubelli, R. (1989). Selective spatial attention and length representation in normal subjects and in patients with unilateral spatial neglect. *Brain and cognition, 9(1),* 57-70.

Pérennou, D. (2006). Postural disorders and spatial neglect in stroke patients: A strong association. *Restorative Neurology and Neuroscience, 24(4-6),* 319-334.

Pérennou, D., Mazibrada, G., Chauvineau, V., Greenwood, R., Rothwell, J., Gresty, M.A., & Bronstein, A.M. (2008). Lateropulsion, pushing and verticality perception in hemispheric stroke: a causal relationship? *Brain, 131,* 2401-2413.

Pizzamiglio L, Vallar G, & Doricchi F. (1995). Gravity and hemineglect. *NeuroReport, 7*, 370 –371.

Robertson, I.H., & Manly, T. (1999). Sustained attention deficits in time and space. In G.W. Humphreys, J. Duncan & A. Treisman (Eds.), Attention, space and action: Studies in cognitive neuroscience (pp. 297-310). Oxford, UK: Oxford University Press.

Robertson, I.H., Mattingley, J.B., Rorden, C., & Driver, J. (1996). Phasic alerting of neglect patients overcomes their spatial deficit in visual awareness. *Nature, 395,* 169-172.

Robertson, I. H., Tegner, R., Tham, K., Lo, A., & Nimmo-Smith, I. (1995). Sustained attention training for unilateral neglect: theoretical and rehabilitation implications. *Journal of Clinical and Experimental Neuropsychology, 17*, 416-430.

Saj, A., Honoré, J., Bernati, T., Coello. Y., & Rousseaux, M. (2005). Subjective visual vertical in pitch and roll in right hemispheric stroke. *Stroke, 36*, 588-591.

Saj, A., Honoré, J., Bernati, T., Richard, C., & Rousseaux, M. (2008). Reducing rightward bias of subjective straight ahead in neglect patients by changes in body orientation. *Journal of Neurology, Neurosurgery, and Psychiatry, 79(9),* 991-996.

Saj, A., Honoré, J., Davroux, J., Coello, Y., & Rousseaux, M. (2005). Effect of posture on the perception of verticality in neglect patients. *Stroke, 36*, 2203-2205.

Sakata, H., Taira, M., Kusunoki, M., Murata, A., & Tanaka, Y. (1997). The parietal association cortex in depth perception and visual control of hand action. *Trends in Neuroscience, 20*, 350-357.

Snyder, L.H., Batista, A.P., & Andersen, R.A. (1997). Coding of intetion in the posterior parietal cortex. *Nature, 386,* 167.

Sturm, W., de Simone, A., Krause, B. J., Specht, K., Hesselmann, V., Radermacher, I., et al. (1999). Functional anatomy of intrinsic alertness: evidence for a fronto-parietal-thalamic-brainstem network in the right hemisphere. *Neuropsychologia, 37*(7), 797-805.

Sturm, W., Schmenk, B., Fimm, B., Specht, K., Weis, S., Thron, A., et al. (2006). Spatial attention: more than intrinsic alerting? *Experimental Brain Research, 171*, 16-25.

Sturm, W., & Willmes, K. (2001). On the functional neuroanatomy of intrinsic and phasic alertness. *Neuroimage, 14*, S76-84.

Tartaglione, A., Benton, A.L., Cocito, L., Bino, G., & Favale, E. (1981). Point localisation in patients with unilateral brain damage. *Journal of neurology, 44,* 935-941.

Tartaglione, A., Cocito, L., Bino, G., Pizio, N., & Favale, E. (1983). Further evidence for asymmetry of point localization in normals and unilateral brain damaged patients.

Neuropsychologia, 21, 407-412.

Taylor, A.M., & Warrington, E.K. (1973). Visual discrimination in patients with localized cerebral lesions. *Cortex, 9,* 82-84.

Thimm, M., Fink, G. R., Kust, J., Karbe, H., & Sturm, W. (2006). Impact of alertness training on spatial neglect: a behavioural and fMRI study. *Neuropsychologia, 44*, 1230-1246.

Vallar, G. (1993). The anatomical bases of spatial neglect in humans. In I.H. Robertson, J. Marshall (Eds.), Unilateral Neglect: Clinical and Experimental Studies (S. 27-53). Hove, UK: Lawrence Erlbaum Associates.

Vallar, G. (1997). Spatial frames of reference and somatosensory processing: a neuropsychological perspective. *Philosophical Transactions of the Royal Society, London B, 352*, 1401-1409.

Warrington, E.K., & James, M. (1967). Disorders of visual perception in patients with localised cerebral lesions. Neuropsychologia, 5, 253-266.

Wilson, B., Cockburn, J., & Halligan, P.W. (1987). Behavioral inattention test. Bury St. Edmunds, UK: Thames Valley.

Yelnik, A. P., Lebreton, F. O., Bonan, I. V., Colle, F., Meurin, F. A., Guichard, J. P., & Vicaut, E. (2002). Perception of Verticality After Recent Cerebral Hemispheric Stroke. *Stroke*, *33*, 2247-2253.

2.2. Effects of lateral head inclination on multimodal spatial orientation judgments in neglect: Evidence for impaired spatial orientation constancy

Funk, J., Finke, K., Mueller, Utz, K.S., & Kerkhoff, G. (2010b).

Neuropsychologia, 48(6), 1616-1627.

2.2.1. Abstract

Recent research revealed that patients with spatial hemi-neglect show deficits in the judgment of the subjective vertical and horizontal. Systematic deviations in the subjective axes have been demonstrated in the visual and tactile modality, indicating a supramodal spatial orientation deficit. Further, the magnitude of the bias was shown to be modulated by head- and body position. The present study investigated the effect of passive lateral head inclination on the subjective visual and tactile vertical and horizontal in neglect patients, control patients with left- or right-sided brain damage without neglect and healthy controls. Subjects performed visual- and tactile-spatial judgments of axis orientations in an upright head orientation and with lateral head inclination 25° in clockwise (CW) or counterclockwise (CCW) direction. Neglect patients displayed a marked variability as well as a systematic tilt in their spatial judgments. In line with a multisensory spatial orientation deficit their subjective vertical and horizontal was tilted CCW in the visual and in the tactile modality, while such a tilt was not evident in any other subject group. Furthermore, lateral head inclination had a differential effect in neglect patients, but not in control subjects. Neglect patients' judgments were modulated in the direction of the head tilt ('A-effect'). That is, a CCW inclination further increased the CCW spatial bias whereas a CW inclination decreased the spatial bias and thus led to approximately normal performance. The increased A-effect might be caused by a pathologically strong attraction of the subjective vertical by an idiotropic vector relying on the actual head orientation, as a consequence of impaired processing of gravitational information in neglect patients.

Keywords: neglect, space perception, subjective vertical, subjective horizontal, visual, tactile, posture, gravity;

2.2.2. Introduction

Hemispatial neglect is a supramodal neurological disorder characterized by a complex syndrome of sensory, motor and representational deficits (for a review, see Kerkhoff, 2001). Neglect patients fail to detect or respond to stimuli in their contralesional hemispace (Bisiach, Pizzamiglio, Nico, & Antonucci, 1996), show unilateral spatial representational deficits (Bisiach & Luzatti, 1978; Bisiach, Capitani, Luzatti, & Perani, 1981) and frequently display a reduced use of their contralesional extremities (Laplane & Degos, 1983). Most of the current models of neglect focus on the explanation of deficits in the horizontal plane. Such deficits are apparent, for example, as left-sided omissions in visual search, reading, writing and drawing tasks, as deficits in (horizontal) size perception in the contralesional hemispace (Milner & Harvey, 1995; Milner, Harvey, Roberts, & Forster, 1993), as a compression of contralesional hemispace (Gainotti & Tiacci, 1971; Nichelli, Rinaldi, & Cubelli, 1989) or even both hemispaces (Halligan & Marshall, 1991), as rightward deviations in line bisection and in pointing straight ahead, and as a deviation of space representation towards the ipsilesional hemispace (Karnath, 1997). However, numerous studies have demonstrated deficits in visuospatial perception and visuomotor performance that cannot result solely from impairments restricted to the horizontal plane (for a review, see De Renzi, 1982). These include impairments in visual orientation discrimination and position estimation (Warrington & James 1967; Taylor & Warrington 1973; Tartaglione, Benton, Cocito, Bino, & Favale, 1981; Tartaglione, Cocito, Bino, Pizio, & Favale, 1983) as well as deficits in the judgment of the subjective visual vertical (SVV) and horizontal (SVH; Howard, 1982; Lenz 1944), and judgments of oblique line orientations (Benton, Hannay, & Varney, 1975; De Renzi, Faglioni, & Scotti, 1971; Kim, Morrow, Passafiume, & Boller, 1984).

Brain damage, hemineglect, and tilted space

The relation between brain damage and deviations of the subjective vertical and, thus, spatial judgments in the frontal plane, was studied extensively by Bender and Jung already in 1948. The authors found that deviations of the subjective vertical from the true vertical exceeding 2° are indicative of frontal or parietal, but not of occipital lobe lesions. The direction of the deviations was contralesional, with clockwise (CW) deviations following left, and counterclockwise (CCW) deviations following right fronto-parietal lesions. In a more recent large-scale investigation, Brandt et al. (1994) tested judgments of the SVV in 71 patients with unilateral hemispheric lesions. MRI analyses revealed that the most impaired patients had lesions centering on the human homologue of the monkey parieto-insular-vestibular cortex (PIVC; Grüsser et al., 1990), and thus closely neighboring and overlapping with those lesions which cause neglect behavior. Hence, it may be mainly the neglect patients who show abnormal SVV judgments in the frontal plane. Accordingly, Kerkhoff and Zoelch (1998) found that 12 out of 13 neglect patients showed deficits in visuospatial judgments of axis orientations in the vertical, horizontal and oblique orientation. The deficits were not an unspecific consequence of brain damage, as patients with left or right hemispheric lesions *without* neglect performed at the level of healthy participants. Furthermore, Yelnik and colleagues (2002) showed that deviations of the SVV are above all related to the neglect severity, rather than to the lesion size and localization, indicating that SVV tilt is not a consequence of right hemisphere damage per se, but rather of anatomical damage which typically causes spatial neglect, including the gravity system of the right hemisphere. These findings indicate a severe disturbance in the representation of space in the frontal plane in neglect patients which does not seem to constitute an epiphenomenon but one of the core deficits of the neglect syndrome.

De Renzi, Faglioni, and Scotti (1971) found that patients with right posterior lesions are significantly impaired in both the visual and the tactile perception of the horizontal and the vertical axis. Kerkhoff (1999) additionally showed that CCW tilts in the two modalities are correlated with each other and with the neglect severity. Thus, comparably to impairments in the horizontal plane, the deficits in the frontal plane seem to be multimodal (or even supramodal). In a recent study with 80 stroke patients, Pérennou et al. (2008) found that patients with right hemisphere lesions showed CCW visual (in 55% of the subjects), tactile (32.5%) and postural (42%) tilts in the frontal plane. Since especially parietal lesions caused marked visual and tactile tilts in the frontal plane, the authors concluded that the right parietal cortex is crucially involved in the elaboration of an internal supramodal model for verticality perception.

Effects of posture and head orientation in space on orientation judgments in neglect

Evidence from recent research suggests that deficits in spatial orientation judgments are significantly modulated by gravitational input in neglect patients. These studies modulated the body posture of neglect patients and, as a consequence, also their head orientation in space to investigate the effect of the accompanying modulations of gravitational information on spatial deficits in these patients. Saj, Honoré, Davroux, Coello, and Rousseaux (2005b) systematically investigated the effects of body posture on the perception of the visuohaptic subjective vertical in the frontal plane. Posture had no effect on SVV judgments in healthy control subjects. However, in the neglect patients the CCW tilt of SVV judgments was significantly reduced in supine compared to upright posture. In supine posture, the influence of otholitic input on space perception is reduced (Diener & Dichgans, 1988; Howard, 1982). Since in neglect patients graviceptive input from the left and right otholitic system is not processed symmetrically (e.g. Pizzamiglio et al., 1995), the change of head position in space in supine compared to upright posture and the accompanying modulation of graviceptive input resulted in a reduction of the pathological bias. Positive effects of modulations of graviceptive input in backward-tilted or lying body position have also been documented for line bisection deviations (Pizzamiglio, Vallar, & Doricchi, 1995) and exploration biases (Karnath, Fetter, and Niemeier, 1998) in neglect patients. In a recent study (Funk et al., 2010), we investigated effects of posture on the subjective *tactile* vertical (STV) in neglect patients and found that posture affects performance of neglect patients also in the spatial domain (although we found different results than Saj et al., 2005b). Apart from whole-body changes, head tilts alone modulate gravitational input and thus also affect spatial orientation judgments in neglect. A further experiment in the Kerkhoff (1999) study showed that the orientation deficit of a neglect patient was significantly aggravated by a CCW tilt of the head by 25°, and significantly reduced by a comparable CW tilt. In a healthy control subject, in accordance with previous evidence (for a review, see Howard, 1986), CW and CCW head tilt slightly deteriorated performance when compared with the upright condition. While these findings indicate that the head-on-trunk orientation (i.e., the angle of inclination) might play an important role in the judgment of spatial orientation in the frontal plane in neglect patients, a more systematic study including a group of patients and controls has not been carried out to date.

Which cues are mediating the effects of posture on spatial orientation?

Different reference frames can define a visual orientation in space (for reviews, see, e.g., Howard, 1982; Rock, 1990; Wade, 1992). Most important for the judgment of the subjective main spatial axes are probably the gravitational and the egocentric (head-/body-centered) reference frames. In upright posture, the gravitational and the egocentric vertical are aligned; by contrast, in tilted head-/body-position, the two coordinate systems are decoupled. Therefore, tilts of the head and body can induce displacements in the *subjective* vertical

(Luyat et al., 2001; Luyat & Gentaz, 2002) either in the direction of postural inclination (the Aubert, or A effect) or in the opposite direction (the Müller, or E effect). It has been suggested that the E effect occurs at small, and the A effect at greater angles of tilt (for a review, see Howard, 1986). However, when the tilt is restricted to the head (with stable position of the body), results vary between experiments, that is, E effects (e.g. Day & Wade, 1969; Wade, 1968), A effects (e.g. Dichgans et al., 1974; Parker et al., 1983) or no general effect (e.g. DiLorenzo & Rock, 1982) were observed. Luyat and Gentaz (2002) argue that "… A and E effects demonstrated that tilted subjects have not access to a veridical gravitational reference frame but rather to a subjective gravitational reference frame which is no longer congruent with the physical one. In the visual modality for example, a rod aligned with the physical vertical will be perceived as deviated in the direction opposite of the head or body tilt (A-effect) and, as a result, the subjective vertical, in this case, will be deviated in the direction of the head or body" (p. 1004, first paragraph). In healthy subjects, the subjective vertical is congruent with the physical/objective one in upright posture and, thus, a displacement in either direction would mean a slight decline in performance. By contrast, in neglect patients, the subjective vertical is *not* congruent with the objective one in upright posture (e.g. Kerkhoff & Zoelch, 1998; Kerkhoff, 1999), probably due to asymmetric processing of gravitational input. In such patients, a further CCW displacement of the subjective vertical would represent a further increase in spatial bias, whereas a CW displacement would represent a decrease in spatial bias and thus a trend towards normal performance.

It has been suggested that the effect of head orientation on the perception of space is based on a modulation of gravitational inflow (e.g. changes in vestibular and kinesthetic inputs; Howard, 1982). More specifically, head inclinations reduce the impact of gravitational input (due to reduced sensitivity of the utricles). Since neglect patients process graviceptive information in an asymmetric way (e.g. Pizzamiglio et al., 1995), this gravitational model predicts a reduction of the spatial bias no matter whether the head is tilted CW or CCW. Conversely, in normal subjects, the model would predict a slightly worse performance with head tilt in either direction. Alternatively, Mittelstaedt (1983) suggested that the subjective vertical is the product of a sensory, a gravitational and an idiotropic vector. In this model, the idiotropic vector (i.e., the body- and head-vertical axis) serves as an intrinsic reference frame guiding spatial orientation. Since neglect patients process graviceptive information deficiently, they might rely more on other information, such as the idiotropic vector, than normal subjects. In this case, the model would predict that neglect patients show a tendency to orient verticality judgments towards the head-vertical axis (A-effect). That is, neglect patients would display an even greater CCW tilt of their subjective vertical with a CCW head tilt and a reduction of the CCW bias with CW head tilt. Healthy subjects might display this tendency too, albeit to a significantly lesser degree.

Rationale of the present study

The present study systematically investigated whether and how spatial orientation deficits are modulated by changes in head orientation in neglect patients. Since head tilt has been shown to modulate gravitational input (e.g., Diener & Dichgans, 1988; Howard, 1982), and furthermore the processing of graviceptive information is known to be deficient in patients with spatial neglect (e.g., Lafosse, Kerckhofs, Troch, Santens, & Vandenbussche, 2004; Pérennou, 2006; Pizzamiglio et al., 1995), we hypothesized that head-on-trunk orientation affects spatial orientation judgments in neglect patients in a different way than in healthy participants and in patients without neglect. Such a differential modulation of performance by head inclination was already demonstrated by Kerkhoff (1999) in a single patient. However, since this pilot study only investigated one single neglect patient and one control subject, it is not clear whether the observed pattern of results is representative for all patients with left spatial neglect or all healthy control subjects and whether the differential modulation of performance as a function of head inclination is characteristic for all patients with right hemisphere damage or exclusively for neglect patients. Therefore, the present, more comprehensive investigation went beyond this demonstration by analyzing visual-spatial and tactile-spatial axis orientation performance in a group study including patients with right hemispheric lesions and left spatial neglect, patients with right or left hemispheric lesions without spatial neglect and healthy control subjects. We predicted that: (1) Neglect patients, but not LBD or RBD controls, would display a multimodal orientation deficit with similar impairments in tactile- as in visual-spatial orientation. That is, they were assumed to display a CCW tilt of the subjective vertical and horizontal in both modalities (Kerkhoff, 1999). Furthermore, we predicted that (2) axis orientation performance in neglect patients would be substantially affected by CW and CCW head inclination, whereas in healthy subjects and control patients without neglect, performance was expected to deteriorate only slightly, if at all. More specifically, a replication of Kerkhoff's (1999) original single-case results would become manifest in terms of an increased A-effect in neglect patients leading to a further performance deterioration with CCW and an improvement with CW head tilt. Such a finding would indicate that neglect patients set the subjective vertical in the direction of the idiotropic vector (Mittelstaedt, 1983). Alternatively, neglect patient's performance could generally improve independently of the direction of head tilt. Such a result would support the gravitational inflow model, since it would indicate that with reduced impact of the disturbed graviceptive information neglect patients' spatial bias is ameliorated. In order to test the two alternative models in the present study, two aspects of spatial performance were analyzed: the difference thresholds (half of the range in which the spatial judgments of subjects varied), which is an indicator for the uncertainty and instability of the spatial representation, and the constant errors (mean value of positive and negative deviations) which indicates the magnitude and direction of the spatial bias. The gravitational inflow model would predict a reduced magnitude of the spatial bias, that is, both difference thresholds and constant errors should be reduced with head tilt. The idiotropic vector model assuming an increased A-effect would predict increased constant errors with a CCW head tilt and reduced constant errors with a CW head tilt, but would not predict changes in the difference thresholds.

2.2.3. Methods

Participants

Eight patients with right hemispheric vascular lesions and left spatial neglect documented by clinical tests (see below), eight patients with right hemispheric vascular lesions and eight patients with left hemispheric lesions without spatial neglect in these tests (further referred to as RBD or LBD controls or more generally as control patients) and eight healthy control subjects were tested. Informed consent according to the Declaration of Helsinki II was obtained from all subjects. Table 1 summarizes the demographic and clinical data. The mean age was 49.5 years (range: 38-64) for the neglect patients, 49.6 years (range: 25-62) for the RBD controls, 50.3 years (range: 39-63) for the LBD controls and 51.0 years (range: 32-67 years) for the healthy controls. Age was not significantly different among the four subject groups ($df=3$, $F=0.04$, $p>0.95$, n.s.) and there was no significant difference in the distribution of gender (assessed via the coefficient of contingency; $\Phi = 2.30$, $p>0.50$, n.s.). The time since lesion was similar in the RBD and LBD controls, but slightly longer in the neglect group (neglect group: 8.8 months, RBD controls: 5.1 months; LBD controls: 5.1 months; $df=2$, $F=3.77$, $p<0.05$). Patients were only included in the sample if they had a single, vascular right or left hemispheric lesion and no evidence of a brain stem lesion as revealed by CT/MRI and clinical symptoms. All subjects were right-handed according to their verbal report.

Table 1: Summary of clinical and demographic data of the neglect patients and the control patients with left- or right-sided brain damage without neglect.

Group	Age	Sex	Etiology	Lesion	TSL (months)	Motor Deficit	Visual Field	Neglect Dyslexia	Figure Copy	Cancell. L/R	Line Bisection
N+	49	1	R-MCA	P-T	12	Plegia	L-Quan	yes	-/+	8/3	+22
N+	43	0	R-MCA	P-T	11	Paresis	L-Quan	yes	-/+	9/4	+15
N+	44	1	R-MCA	P-T	10	Plegia	L-Quan	yes	-/+	6/4	+9
N+	64	1	R-MCA	P-T	4	Paresis	Normal	yes	-/+	3/0	+8
N+	59	0	R-PCA	P-Thal	9	Paresis	L-HH	yes	-/+	5/2	-12
N+	38	0	R-MCA	P-T	9	Paresis	L-Quan	yes	-/+	7/2	-17
N+	50	1	R-MCA	P-T	13	Plegia	Normal	yes	-/+	8/5	+12
N+	49	0	R-ICB	BG	2	Paresis	Normal	yes	-/+	7/1	+33
LBD	41	1	L-MCA	F-P	9	Paresis	Normal	Aphasia	+/+	0/0	-1
LBD	63	1	L-MCA	P-T	4	Paresis	Normal	Aphasia	+/+	0/0	0
LBD	53	1	L-MCA	P-T	5	Paresis	Normal	Aphasia	+/+	0/0	0
LBD	45	0	L-MCA	P-T	8	Paresis	Normal	Aphasia	+/+	0/0	+2
LBD	56	0	L-MCA	F-T	5	Paresis	Normal	Aphasia	+/+	0/0	-3
LBD	56	0	L-PCA	O-T	3	Normal	R-Quan	no	+/+	0/0	+2
LBD	39	0	L-MCA	F	5	Paresis	Normal	Aphasia	+/+	0/0	-2
LBD	49	0	L-MCA	P-T	2	Normal	Normal	Aphasia	+/+	0/0	-2
RBD	50	1	R-MCA	T	5	Paresis	L-Quan	no	+/+	0/0	+1
RBD	48	1	R-ICB	T-P	5	Paresis	Normal	no	+/+	0/0	-1
RBD	46	0	R-MCA	P	9	Paresis	Normal	no	+/+	0/0	+2
RBD	62	0	R-MCA	P-T	9	Plegia	L-HH	no	+/+	1/0	-22
RBD	55	0	R-MCA	P-T	3	Plegia	Normal	no	+/+	0/0	-2
RBD	57	0	R-ICB	BG	5	Paresis	Normal	no	+/+	0/0	-2
RBD	25	0	R-MCA	T	4	Paresis	L-Quan	no	+/+	0/0	+2
RBD	54	0	R-MCA /PCA	P-O	1	Normal	L-HH	no	+/+	0/1	+3

Abbreviations: N+, neglect patient; LBD, left brain damaged control patient; RBD, right brain damaged control patient; Etiology: MCA/PCA, middle/posterior cerebral artery infarction; ICB, intracerebral bleeding; L/R, left/right; Lesion: F, frontal; P, parietal; T, temporal; O, occipital; BG, basal ganglia; Thal, thalamus; TSL: time since lesion; Visual Field: HH, homonymous hemianopia; Quan, homonymous quadrantanopia; Neglect screening tests: Neglect Dyslexia: 180 word reading test, cutoff: max 2 errors, yes/no: neglect dyslexia present/absent, aphasia: reading not tested due to aphasia (documented by the Aachener Aphasie Test); Figure Copy: **-** = omissions or distortions; + = normal performance; Cancellation: number of omissions per hemispace, cutoff: max 1 per hemispace; Horizontal Line Bisection: deviation from true midline in mm to left (-) or right side (+).

Neglect tests

All patients underwent a screening for visual neglect including horizontal line bisection of a 20 x 1 cm black line presented on white paper, representational drawing of a star, a daisy, a clock, a house and a face, and number cancellation on white paper (size 29.7 x 14.7 cm; 10 targets in each hemispace among 100 numbers on the total page). In addition, a 180 word reading test sensitive to neglect and hemianopic reading disturbances (Kerkhoff et al., 1992) was administered. Cutoffs were deviations of more than 5 mm from the true midpoint of a 20 cm line in line bisection, more than 1 omission in each hemispace in the number cancellation task, and more than two omissions or substitutions of letters or words and/or prolonged reading times (> 120 sec). Furthermore, omissions or significant distortions of the right half of the copied figures was interpreted as an indicator of hemispatial neglect.

Visual-spatial tests

Figure 1A displays the visual spatial orientation tasks. The subjects were tested using specific software (termed VS; Kerkhoff & Marquardt, 1995b) for the measurement of the SVV and SVH. VS is based on the method of limits (Engen, 1971). In the subtests measuring the SVV and SVH, the experimenter successively rotates an oblique white line (18 x 1.4 cm) presented on a dark background until the subject indicates that it lies exactly vertically or horizontally. With this method, two psychophysical parameters were calculated: the constant error and the difference threshold. The constant error denotes the difference between the subject´s mean estimate (the point of subjective equality) and the objective correct orientation. Hence, the constant error gives information about the central tendency or central error of the subject. The interval of uncertainty indicates the complete range within which the subject considers the displayed line as exactly vertical, horizontal or parallel in the oblique task. From this value the difference threshold is calculated, which is defined as one-half of the interval of uncertainty.

Constant errors and difference thresholds were computed by the software as described above. The step-width was 0.5° in all measurements.

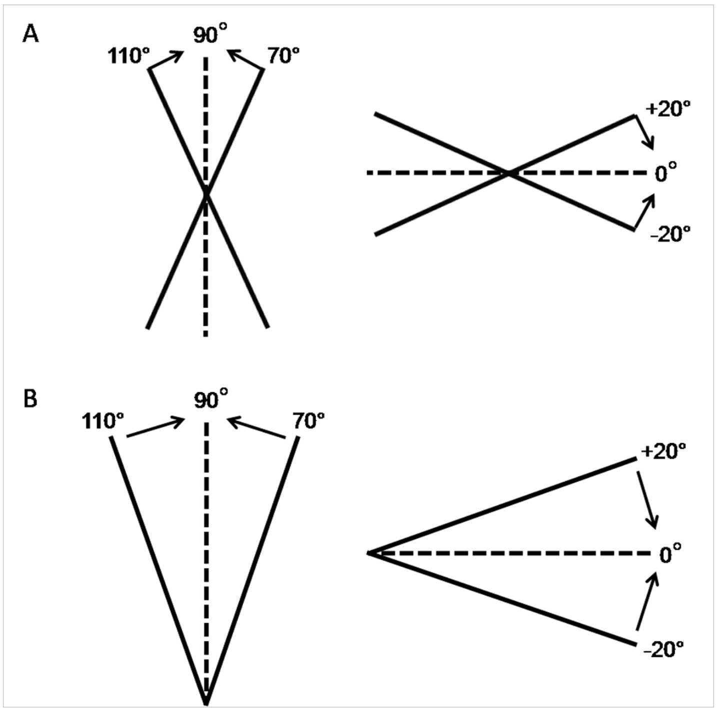

***Figure 1** A, B:* Experimental setup in the spatial orientation tasks for the visual (fig. 1A) and tactile (fig. 1B) modality. Subjects were presented with a line on a computer screen (visual condition) or a metal rod (tactile condition) which they had to adjust to their subjective vertical or horizontal. The tests were performed in total darkness (visual condition) or with the subject blindfolded (tactile condition).

Tactile-spatial tests

The tests for the subjective tactile axes (vertical = STV and horizontal = STH) were performed using a rotatable bar (15 cm long, 12 mm wide) which was mounted on a plate and could be rotated in 1°-steps along the frontal plane (see Fig. 1B). The plate (50 x 50 cm) was mounted vertically in front of the patient. A scale, concealed from the subject, was drawn on the plate to record the orientation measurements (0°=right horizontal, 90°=vertical, 180°=left horizontal). Participants' task was to adjust the metal rod to their STV and STH. Healthy controls used their right, dominant hand and brain-damaged patients used their ipsilesional hand. Subjects were not allowed to touch the outer surface of the test plate, so as to eliminate any horizontal and vertical reference cues. Before each testing session, the apparatus was calibrated to the gravitational vertical. As for the visual axes, constant errors and difference thresholds were calculated for the STV and STH.

Testing conditions

Visual-spatial measurements were taken in total darkness with the chassis of the PC-monitor covered by an oval-shaped mask to eliminate any visual reference cues. Subjects were tested at a distance of 0.5 m from the monitor, with corrected-to-normal vision where necessary. The tactile-spatial tests were performed at the same distance with subjects blindfolded before starting the practice trials. Visual- and tactile-spatial tests were administered under three experimental conditions: with the subjects' heads upright (0° head tilt), or with the heads tilted 25° CW or CCW. The trunk remained vertical in all conditions and head position in the pitch-plane (fore-back-dimension) was always stabilized by a head-and-chin-rest (see below). Lateral head inclination was achieved by positioning the subjects' heads in a tiltable head-and-chin-rest (tiltable in the frontal plane) which was fixed to an experimental table (see figure 2). Ten trials were presented for each spatial orientation and modality. The sequence of the tests (i.e., spatial orientation and modality) was counterbalanced to avoid systematic practice effects. In all conditions, starting position was 20° away from the vertical / horizontal axis. The direction (CW, CCW) of the initial tilt was balanced throughout all tests to reduce effects of rotation direction. Prior to the completion of valid trials, subjects were familiarized with the experimental setup in each condition and performed five practice trials.

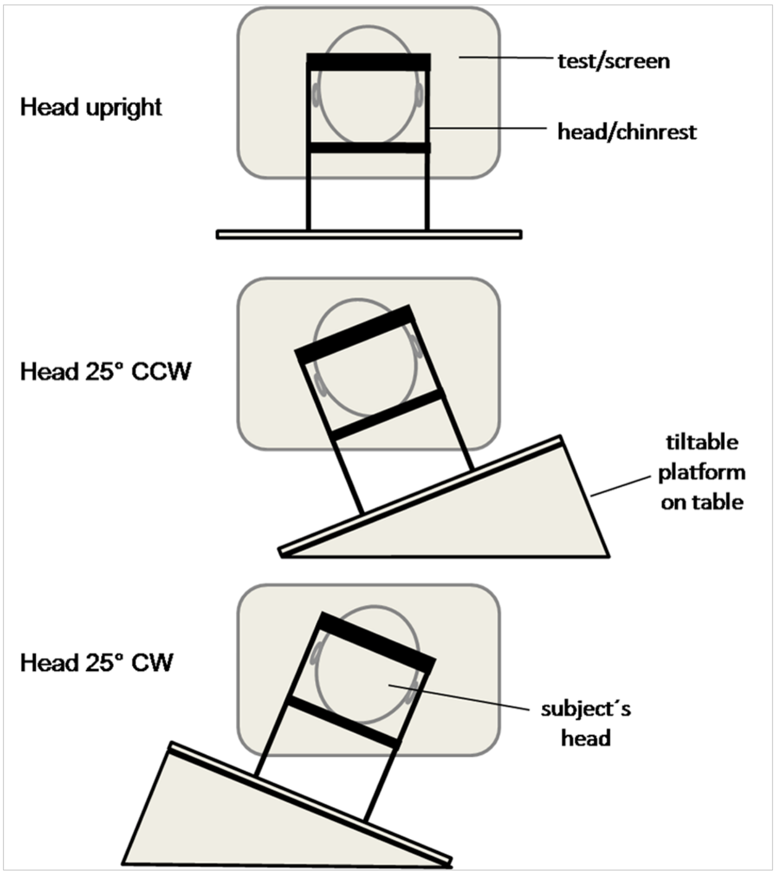

Figure 2*:* Experimental setup in the visual- and tactile-spatial tests in three head orientation conditions: with the subject's head upright (0° head tilt), or with the head tilted 25° CW or CCW; head position was modulated and stabilized by a tiltable head-and-chin-rest; the head-and-chin-rest was attached to the experimental table (upright head condition) or to a wedge-shaped block on the table (CW or CCW head orientation condition).

Statistics

For constant errors and difference thresholds, repeated-measures ANOVAs (with subject group and head orientation as factors) were performed to analyze spatial performance separately for the SVV and SVH and the STV and STH. In case of significant main effects or interactions, subsequent post-hoc comparisons were calculated: post-hoc Scheffé tests were used to compare performance between subject groups; one-way ANOVAs and contrasts (where necessary) were used to compare performance between head orientation conditions within one subject group. To further investigate the general direction of tilt, that is, systematic deviations from zero in the constant errors, one-sample t-tests were calculated for each subject group. The alpha-level was chosen as $p<0.05$ for all analyses.

2.2.4. Results

Neglect tests

The data of each patient in the neglect tests are summarized in table 1. All neglect patients showed impaired copying performance, with the typical omissions and/or distortions of the left side of the drawings, as well as impaired reading performance indicating neglect dyslexia. They also showed the characteristic pattern of omissions in the number cancellation task, with significantly more omissions in the left compared to the right hemispace [mean omissions: 6.6 in the left and 2.6 in the right hemispace; $t(7)=8.00$, $p<0.01$]. Furthermore, six out of eight patients showed the typical rightward deviation in horizontal line bisection; two patients (both with left-sided visual field defects) showed leftward deviations (mean deviation: 8.8 mm to the right). Left and right brain-damaged control patients did not show impaired drawing or neglect dyslexia (the latter not measured in aphasic LBDs). They also showed intact performance in the number cancellation task (LBD mean: 0 omissions in left and right hemispace; RBD mean: 0.1 omissions in both left and right hemispace) and only nonsystematic, mostly slight, deviations in line bisection performance (LBD mean: 0.5 mm to the left; RBD mean: 2.4 mm to the left).

Visual- and tactile-spatial orientation judgments

Figure 3a and 3b show the visual- and tactile-spatial orientation judgments in neglect patients and healthy controls as a function of head orientation. The lines within the circles display the mean subjective vertical and horizontal of individual patients and control subjects.

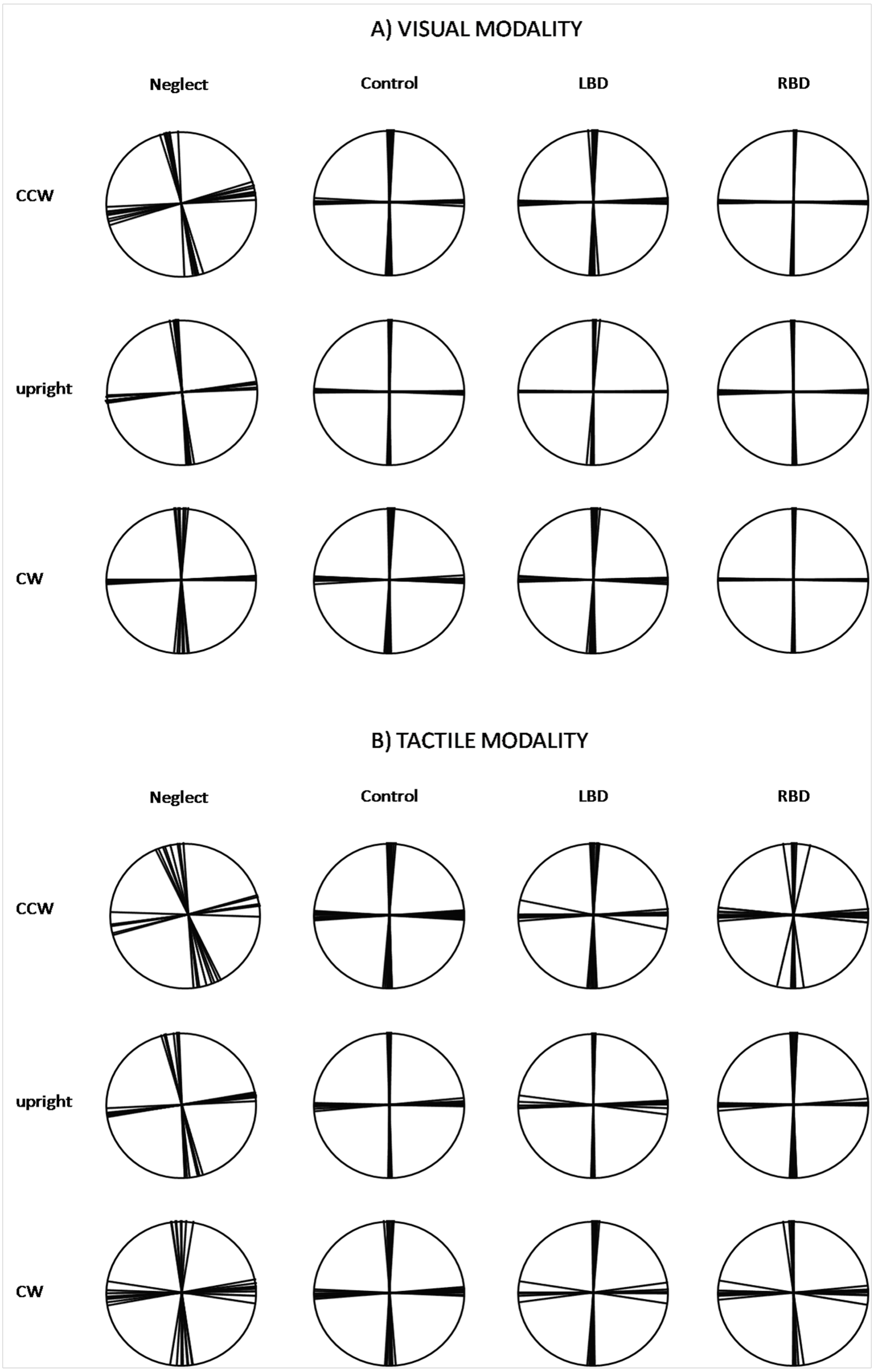

Figure 3 *A, B:* Mean performance of neglect patients, LBD and RBD control patients and healthy controls in the *visual*-spatial (figure 3A) and *tactile*-spatial (figure 3B) orientation task for the three head orientation conditions; CCW, head inclination 25° CCW; upright, vertical head position; CW, head inclination 25° CW; the lines within the circles display the mean SVV and SVH of individual patients and control subjects.

While the normal subjects (and also the RBD and LBD controls not displayed in fig. 3) show only marginal deviations of their visual and tactile subjective vertical and horizontal, neglect patients display a marked and systematic CCW tilt. As can be seen, the severity of the tilt is heterogeneous in the group of neglect patients, while judgments of healthy controls are very accurate. Furthermore, the neglect patients' judgments are substantially modulated by head orientation, whereas healthy controls (and also LBD and RBD control patients) show only minor and nonsystematic effects of head orientation.

General direction of tilt in upright posture

To assess the systematic direction of tilt in the 'normal' orientation condition, one-sample t-tests were calculated for the constant errors of each group in all spatial orientation tests (SVV, SVH, STV and STH) in the upright head orientation condition. Constant errors of healthy, LBD and RBD controls did not differ significantly from zero (all $p>0.10$; n.s.). By contrast, those of neglect patients were significantly larger than zero for all spatial tests (all $p<0.05$), indicating a significant CCW deviation from the optimum orientation. This CCW tilt was shown by all eight neglect patients in the visual-spatial as well as in the tactile-spatial orientation task. That is, under normal conditions neglect patients displayed reliable, substantial and systematic CCW tilts of the visual- and tactile-spatial axes.

Relation between visual and tactile-spatial orientation

The spatial bias in the tactile and visual orientation tests (i.e., the positive constant errors) were compared in repeated-measures ANOVAs with the factors 'group' and 'modality' for the vertical and horizontal axes in the upright head orientation condition. The ANOVA for the subjective vertical revealed a significant effect of group ($df=3$, $F=37.02$, $p<0.01$) and an effect of modality for the vertical axis ($df=1$, $F=4.79$, $p<0.05$), but no interaction of modality with group (*df*=3, *F*=2.29, *p*=0.10, n.s.). Also for the subjective horizontal, a significant effect of group was found (*df*=3, *F*=58.33, *p*<0.01), a significant effect of modality (*df*=1, *F*=4.29, *p*<0.05), but no interaction of group and modality (*df*=3, *F*=0.48, *p*>0.65). For both the vertical and the horizontal, constant errors were generally greater in the tactile condition than in the visual condition. However, as there was no interaction between 'group' and 'modality', the relative pattern of results was equivalent in both modalities.

Effects of head orientation on spatial orientation judgments

Table 2 summarizes the mean constant errors and difference thresholds and the statistical results for each subject group in the visual and tactile subjective vertical and horizontal across the three different head orientation conditions.

Constant errors

Visual vertical and horizontal

Figure 4 displays the mean constant errors of the SVV and SVH for all subject groups. Constant errors were substantially larger in neglect patients compared to all control groups. Furthermore, as can be seen, constant errors were drastically modulated by passive head inclination in neglect patients, that is, they were aggravated by a CCW and reduced by a CW inclination, whereas constant errors varied only marginally in the control groups.

For the *SVV*, the repeated-measures ANOVA (with the factors subject group and head orientation) revealed significant effects of group (*df*=3, *F*=78.57, *p*<0.01) and head orientation (*df*=2, *F*=12.59, *p*<0.01), and a significant interaction of group and head orientation (*df*=6, *F*=10.83, *p*<0.01). Neglect patients generally displayed significantly larger constant errors compared to all control groups (all *p*<0.01), whereas healthy, RBD and LBD controls were comparable to each other (all *p*>0.45, n.s.).

Table 2: Summary of the mean constant errors and difference thresholds and the statistical results (contrasts in post-hoc one-way ANOVAs) for each subject group in the visual and tactile subjective vertical and horizontal across the three different head orientation conditions.

Parameter	Group	Test	CCW 25°	versus	Upright	versus	CW 25°
Constant errors	N+	SVV	10.8	** (>)	5.5	* (>)	0.3
		SVH	9.6	** (>)	6.0	** (>)	1.7
		STV	15.0	** (>)	8.6	* (>)	1.6
		STH	8.5	ns	7.2	* (>)	2.5
	Control	SVV	-0.7	ns	-0.4	ns	-1.6
		SVH	0	ns	-0.4	ns	-0.5
		STV	-0.8	ns	0.2	ns	0.8
		STH	-0.5	ns	0.7	ns	0.9
	RBD	SVV	-1.1	** (<)	0.5	ns	-0.2
		SVH	0	ns	0.4	ns	-0.1
		STV	-0.5	ns	-0.1	ns	1.7
		STH	-1.0	ns	1.2	ns	-0.3
	LBD	SVV	-0.5	ns	-1.5	ns	-1.3
		SVH	0.6	ns	0	ns	-0.2
		STV	-0.9	ns	-0.3	ns	-1.3
		STH	-0.4	ns	-0.1	ns	0.2
Difference thresholds	N+	SVV	5.0	ns	3.5	ns	4.1
		SVH	4.1	** (>)	2.7	ns	2.1
		STV	7.6	ns	8.2	ns	8.6
		STH	6.4	ns	7.1	ns	5.4
	Control	SVV	1.6	ns	1.1	ns	1.5
		SVH	1.1	ns	0.9	ns	1.3
		STV	2.9	ns	2.9	ns	3.1
		STH	3.2	ns	2.5	ns	3.6
	RBD	SVV	2.5	ns	1.9	ns	2.1
		SVH	1.8	ns	1.4	ns	1.6
		STV	4.6	ns	3.6	ns	4.7
		STH	4.4	ns	3.9	ns	3.7
	LBD	SVV	2.4	ns	1.4	ns	2.3
		SVH	2.2	ns	1.0	ns	1.8
		STV	3.2	ns	2.5	ns	4.6
		STH	3.0	ns	2.8	ns	3.2

Abbreviations: CCW 25°, head tilted 25° CCW; Upright, upright head orientation; CW 25°, head tilted 25° CW; N+, neglect patients; Control, healthy control subjects; RBD, right brain damaged control subjects; LBD, left brain damaged control subjects; SVV, subjective visual vertical; SVH, subjective visual horizontal; STV, subjective tactile vertical; STH, subjective tactile horizontal; **: p<0.001; *: p< 0.05; ns: nonsignificant.

One-way ANOVAs revealed that head orientation significantly affected performance in neglect patients (*df*=2, *F*=16.67*, p*<0.01) and in RBD controls (*df*=2, *F*=9.75*, p*<0.01), but not in LBD and healthy controls (both *p*>0.15, n.s.). In neglect patients, a CCW head tilt aggravated the deficit significantly compared with an upright head orientation (*p*<0.01) and, thus, further increased the pathological bias, whereas a CW head tilt improved performance significantly compared to an upright head orientation (*p*<0.05), that is, it reduced the bias. In the RBD controls, a CCW head tilt impaired visual-spatial orientation judgments significantly compared with an upright head orientation (*p*<0.01), while the upright and CW head orientations did not differ significantly from each other (*p*>0.10, n.s.).

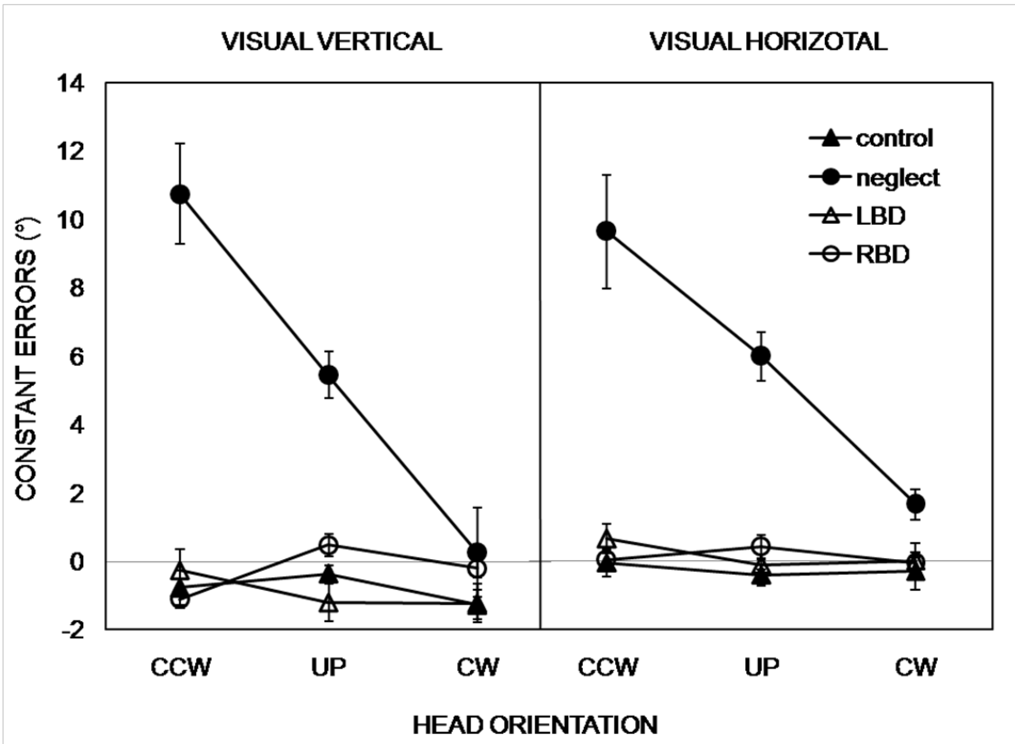

Figure 4: Constant errors (means and standard errors) in the *visual*-spatial orientation task for the three head orientation conditions (CCW, head tilted 25° CCW; UP, upright head orientation; CW, head tilted 25° CW) in neglect patients, healthy control subjects, left brain-damaged control subjects (LBD) and right brain-damaged control subjects (RBD); positive constant errors indicate CCW rotations, negative constant errors CW rotations.

For the *SVH*, significant effects of group (df=3, F=46.78, p<0.01), and of head orientation (df=2, F=16.21, p<0.01), and a significant group-by-head orientation interaction (df=6, F=10.55, p<0.01) were found. Neglect patients generally displayed significantly larger constant errors compared to all control groups (all p<0.01), whereas healthy, RBD and LBD controls did not differ from each other (all p>0.90, n.s.). Separate one-way ANOVAs for the different groups revealed that head orientation significantly affected performance in the neglect patients (df=2, F=16.88, p<0.01), but not in the other groups (all p>0.40, n.s.). In neglect patients, a CCW head tilt aggravated the deficit significantly compared with an upright head orientation (p<0.01) and, thus, further increased the pathological bias, whereas a CW head tilt improved performance significantly compared to an upright head orientation (p<0.01), that is, it reduced the bias.

Tactile vertical and horizontal

Figure 5 displays the average constant errors of the STV and STH for all subject groups. As can be seen, constant errors are substantially larger in neglect patients compared to all other groups. Furthermore, constant errors are drastically modulated by lateral head inclination in neglect patients, that is, they are aggravated by a CCW and reduced by a CW head inclination, whereas constant errors vary only marginally in the healthy controls and the control patients without neglect. For the *STV*, significant effects of group (df=3, F=13.82, p<0.01) and head orientation (df=2, F=5.67, p<0.01) and a group x head orientation interaction (df=6, F=12.26, p<0.01) were found. Neglect patients generally displayed significantly larger constant errors compared to all control groups (all $p<0.01$), whereas those of the control groups were comparable to each other (all p>0.90, n.s.). One-way ANOVAs revealed that in neglect patients, head orientation significantly affected constant errors (df=2, F=16.68, p<0.01): a CCW head tilt aggravated the deficit significantly compared with an upright head orientation

($p<0.01$) and, thus, further increased the pathological bias, whereas a CW head tilt improved performance significantly compared to an upright head orientation ($p<0.05$), that is, it reduced the bias. In the different control groups, constant errors did not differ significantly among head orientation conditions (all $p>0.20$, n.s.).

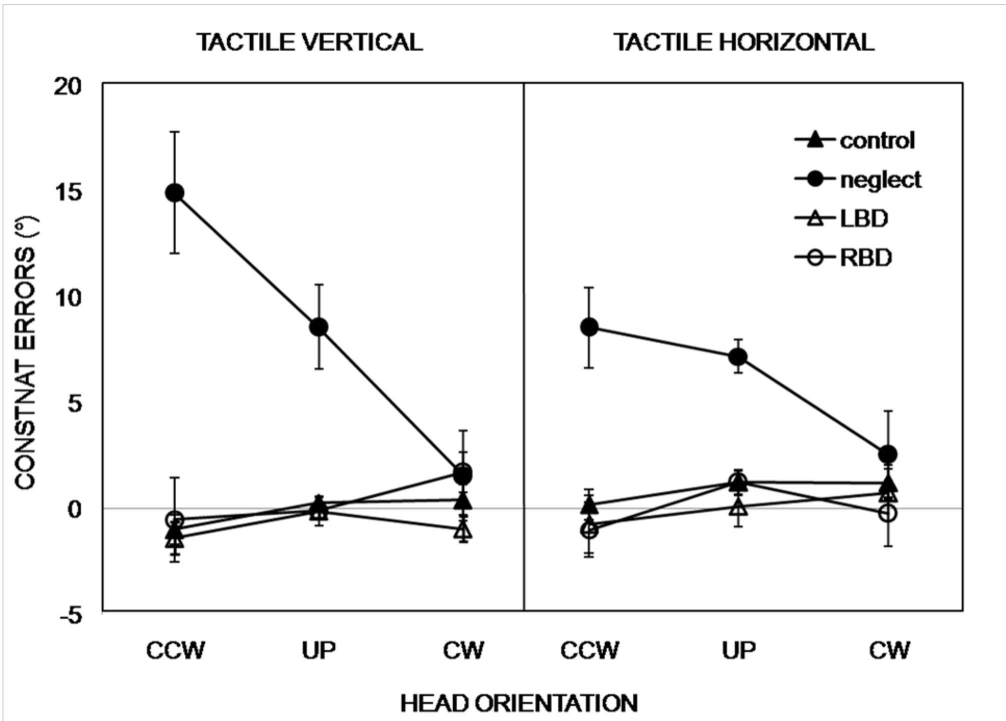

Figure 5: Constant errors (means and standard errors) in the *tactile*-spatial orientation task for the three head orientation conditions (CCW, head tilted 25° CCW; UP, upright head orientation; CW, head tilted 25° CW) in neglect patients, healthy control subjects, left brain-damaged control subjects (LBD) and right brain-damaged control subjects (RBD); positive constant errors indicate CCW rotations, negative constant errors CW rotations.

For the *STH*, the main effect of group ($df=3$, $F=6.70$, $p<0.01$), head orientation ($df=2$, $F=3.41$, $p<0.05$) and the group-by-head orientation interaction were significant ($df=6$, $F=5.44$, $p<0.01$). Neglect patients generally displayed significantly larger constant errors compared to healthy controls and RBD and LBD controls (all $p<0.05$), whereas the other groups did not differ significantly from each other (all $p>0.90$, n.s.). One-way ANOVAs revealed that in the neglect patients, head orientation significantly affected performance ($df=2$, $F=9.22$, $p<0.01$):

a CW head tilt improved performance significantly compared to an upright head orientation ($p<0.05$) and, thus, reduced the pathological bias. There was no significant aggravation of performance with CCW head tilt compared with an upright head orientation ($p>0.30$), but compared with a CW head tilt ($p<0.01$). In healthy, LBD and RBD controls, constant errors did not differ significantly among head orientation conditions (all $p>0.08$, n.s.).

To summarize, constant errors were consistently increased in neglect patients compared to healthy and brain-damaged control subjects. Furthermore, CCW head inclination (by 25°) consistently aggravated the axis orientation deficit in the neglect patients and, thus, increased the pathological bias, whereas CW head orientation improved it relative to upright head orientation, that is, it reduced the bias. In healthy and brain-damaged control subjects, head orientation in few cases had an effect on the constant errors as well. However, the direction of the constant errors did not covary with the direction of head tilt as in the neglect patients.

Difference Thresholds

Visual vertical and horizontal

Figure 6 displays the average difference thresholds of the SVV and SVH separately for each subject group. As can be seen, the certainty of the judgments was decreased in neglect patients compared to the other subject groups, as indicated by generally larger difference thresholds. For the *SVV*, the repeated-measures ANOVA with the factors subject group and head orientation revealed a significant group effect (df=3, F=20.05, $p<0.01$), a significant effect of head orientation (df=2, F=5.15, $p<0.01$), but no significant interaction (df=6, F=0.42, $p>0.85$, n.s.). Neglect patients generally displayed significantly larger difference thresholds compared to all other groups (all $p<0.01$), whereas the control groups did not differ significantly from each other (all $p>0.20$, n.s.). Across subjects, difference thresholds were larger when the head was tilted CW or CCW compared with an upright head orientation (both

$p<0.05$). For the *SVH*, a significant group effect was found (*df*=3, *F*=13.80, $p<0.01$), a significant effect of head orientation (*df*=2, *F*=11.32, $p<0.01$), and a significant group x head orientation interaction (*df*=6, *F*=4.13, $p<0.01$). Neglect patients generally exhibited significantly larger difference thresholds compared to all other groups (all $p<0.01$), whereas the control groups again did not differ significantly from each other (all $p>0.30$, n.s.). One-way ANOVAs revealed that in the neglect patients, head orientation significantly affected performance (*df*=2, *F*=11.02*,* $p<0.01$): a CCW head tilt increased difference thresholds significantly compared with a CW head tilt or an upright head orientation (both $p<0.01$), whereas thresholds did not differ significantly between CW and upright head orientations ($p>0.20$, n.s.). In the control groups, difference thresholds did not differ significantly among the three head orientation conditions (all $p>0.05$, n.s.).

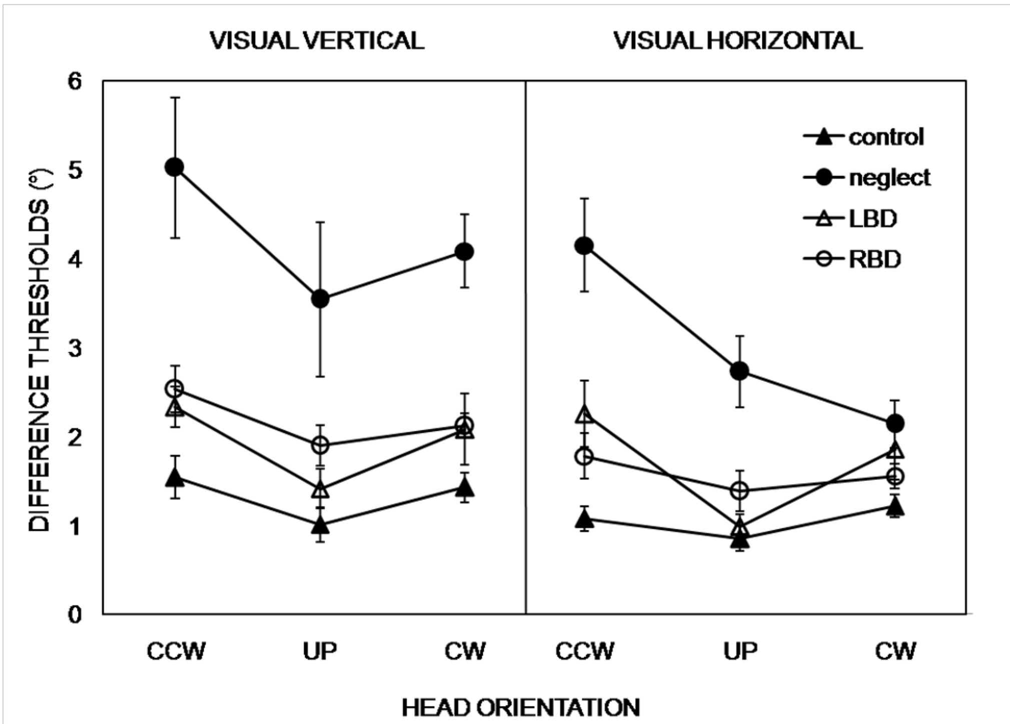

Figure 6: Difference thresholds (means and standard errors) in the *visual*-spatial orientation task for the three head orientation conditions (CCW, head tilted 25° CCW; UP, upright head orientation; CW, head tilted 25° CW) in neglect patients, healthy control subjects, left brain-damaged control subjects (LBD) and right brain-damaged control subjects (RBD).

Tactile vertical and horizontal

Figure 7 displays the difference thresholds of the STV and STH for all groups. As can be seen, those of neglect patients were generally increased compared to the control groups.

For the *STV*, a significant effect of group (*df*=3, *F*=11.36, *p*<0.01), but no effect of head orientation (*df*=2, *F*=1.67, *p*>0.15, n.s.) and no significant group x head orientation interaction (*df*=6, *F*=0.45, *p*>0.80, n.s.) were found. Neglect patients displayed significantly larger difference thresholds compared to all control groups (all *p*<0.01), whereas those of the different control were comparable to each other (all *p*>0.60, n.s.).

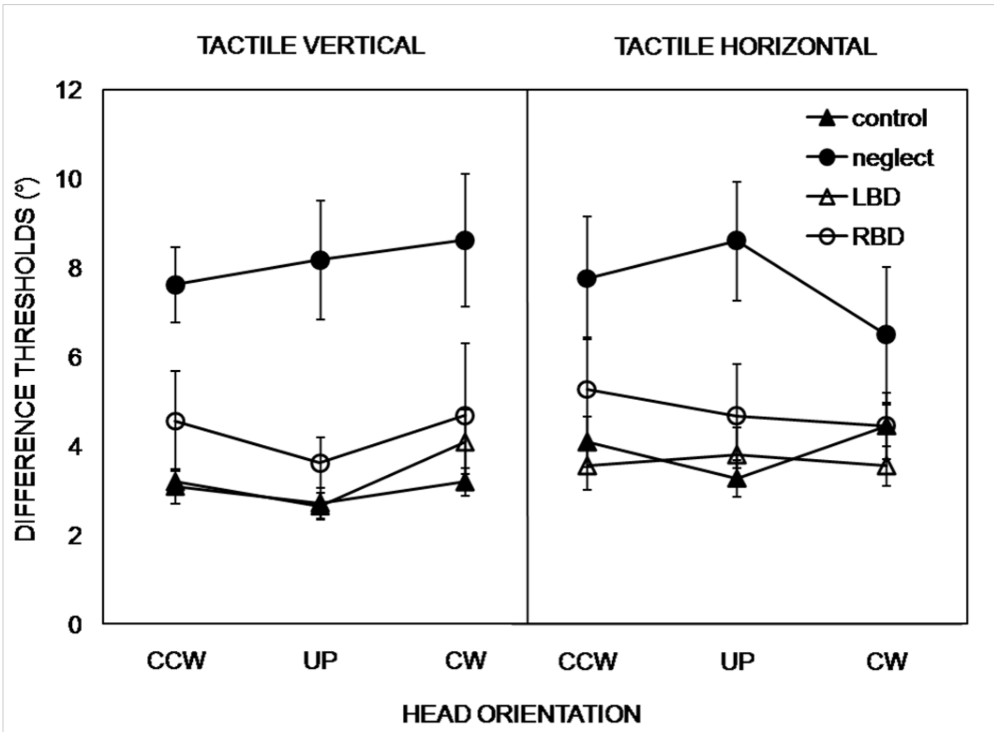

Figure 7: Difference thresholds (means and standard errors) in the *tactile*-spatial orientation task for the three head orientation conditions (CCW, head tilted 25° CCW; UP, upright head orientation; CW, head tilted 25° CW) in neglect patients, healthy control subjects, left brain-damaged control subjects (LBD) and right brain-damaged control subjects (RBD); positive constant errors indicate CCW rotations, negative constant errors CW rotations.

For the *STH*, a significant group effect (*df*=3, *F*=6.19, *p*<0.01), but no effect of head orientation (*df*=2, *F*=0.25, *p*>0.75) or a group- x orientation interaction were obtained (*df*=6,

F=1.23, p>0.30). Neglect patients exhibited significantly larger difference thresholds compared to healthy and LBD controls (all $p<0.05$), but not to RBD controls (p>0.10); the different control groups did not differ significantly from each other (all p>.75, n.s.).

To summarize, difference thresholds were consistently increased in neglect patients compared to healthy controls and brain-damaged control subjects. However, head inclination did not consistently modulate this parameter of uncertainty in the neglect patients in any way other than in healthy or brain-damaged controls.

2.2.5. Discussion

The rationale of the present study was to investigate whether and how multimodal spatial orientation deficits are modulated by head orientation, more specifically, by *lateral* head inclination. Visual-spatial and tactile-spatial axis orientation performance was analyzed in patients with right hemispheric lesions and left spatial neglect, left- and right-brain-damaged control patients without neglect and healthy control subjects. In order to show that neglect patients display a multimodal orientation deficit, we tested whether they show homologous, direction-specific impairments in tactile-spatial orientation as in visual-spatial orientation. Furthermore, we assessed whether axis orientation performance deficits are modulated by variations in gravitational and somatosensory input differently in neglect patients compared to brain-damaged and healthy controls.

Evidence for a supramodal orientation deficit in neglect

In accordance with our prior hypothesis of a multimodal or even supramodal spatial orientation deficit (Kerkhoff, 1999), the neglect patients investigated in the present study showed systematic and analogous tilts of the subjective *visual* and *tactile* vertical and horizontal. The spatial conformity of deviations in the frontal plane in both modalities indicates a disturbed central representation of gravity after parieto-temporal lesions (Brandt et al., 1994). Recently, Pérennou et al. (2008) showed that the most marked visual and tactile tilts in the frontal plane were associated with right parietal lesions, suggesting that an internal model of verticality is elaborated in right parietal cortex. The assumption of the parietal cortex as the anatomical substrate of a supramodal spatial reference frame is further supported by findings indicating the existence of multimodal (e.g. Graziano & Gross, 1995; Duhamel, Colby, & Goldberg, 1998) and 'axis-orientation-selective' (Sakata et al., 1997) neurons in the parietal cortex. Based on single-cell recordings in the monkey parietal cortex, Sakata et al. (1997) identified neurons in the lateral bank of the caudal intraparietal sulcus which are relevant for the coding of axis orientation in three-dimensional space. Since bimodal neurons have been described in the monkey parietal areas (Graziano & Gross, 1995; Duhamel, Colby, & Goldberg, 1998), these neurons might also be activated by the touch of objects with similar spatial orientations. Damage to such multimodal and orientation-selective neurons might be responsible for the deficits in the perception and representation of the principal spatial axes (that become manifest in identical tilts in different modalities). Moreover, cells in the posterior parietal cortex have been reported to contribute to the representation of space by integrating multimodal afferent and reafferent information (Andersen, Essick, & Siegel, 1985). Parietal areas 7a and LIP (lateral intraparietal) have been shown to receive visual signals and eye position signals (Andersen & Mountcastle, 1983; Andersen et al., 1985), as well as efference copies of motor signals, vestibular signals and neck proprioceptive signals (e.g. Bremmer et al., 2002; Brotchie et al., 1995; Snyder et al., 1997) to account for head orientation and head movements in space. Damage to the right posterior parietal cortex might therefore lead to a systematic error in the integration of information – as for example somatosensory (head-position) and graviceptive (vestibular) input – in neglect patients. This is in line with the view that systematic tilts of the coordinate systems can be caused by damage to various parts of a complex system underlying the representation of space, including lesions of the central vestibular pathways (brain stem, thalamus, or vestibular cortex), as well as sensory pathways and (right) parietal lesions (as suggested, e.g., by Brandt et al., 1994). The neglect patients examined in the present study had lesions of structures that are involved in the representation of space, including the parietal or temporo-parietal cortex and in two cases also the thalamus and the basal ganglia.

Differential effects of head tilt on spatial performance

Head orientation significantly and consistently affected the perceptual tilts in the visual and spatial orientation tests only in neglect patients. CCW passive head tilt resulted in a significant aggravation of the spatial bias, that is, in further increased CCW deviations of orientation judgments, whereas CW passive head tilt led to a reduction of the CCW tilt and thus a trend towards normal performance. Our data suggest a significant influence of the head vertical axis in determining the perceptual vertical and horizontal. This influence seems to be much greater in the neglect patients compared to healthy and brain-damaged controls who displayed only small and inconsistent effects. From previous research on the effects of head orientation on the perception of space, two influential models have emerged which assume that such effects reflect gravitational inflow (e.g.; changes in vestibular and kinesthetic inputs – Howard, 1982) and/or the importance of the body- and head-vertical axis as an intrinsic reference in guiding spatial orientation (Mittelstaedt, 1983). According to the gravitational inflow model, effects of head tilt on the subjective vertical are at least partly based on a decrease in otolith sensitivity when the head is inclined, which leads to a reduced impact of graviceptive input on the perception of space. This view is supported by studies demonstrating effects of upright versus supine head orientation on space perception in neglect patients (Pizzamiglio et al., 1995; Saj et al., 2005b; Saj et al., 2008).

The present study investigated spatial performance as a function of *lateral* head inclination (i.e. head orientation was varied in the *frontal* plane). Unlike previous studies, our data reveal a systematic modulation pattern, that is, the direction of head orientation is critical for the direction of the modulation: a CCW head tilt modulated performance in the opposite direction to a CW head tilt. This systematic, orientation direction-specific pattern of results in neglect patients cannot be explained by a general reduction of the impact of gravitational input with head inclination, since a head tilt in either direction should lead to a reduced sensitivity of the utricles and, thus, an ameliorated spatial bias according to the gravitational inflow hypothesis (Howard, 1982). If neglect patients would rely mainly on gravitational information as a reference for their spatial judgments, the present pattern of results could result only if the asymmetry in the processing of gravitational information would be increased or reduced depending on the direction of head orientation; that is, if head inclination in the direction of the spatial bias (i.e., a CCW tilt of the head) would lead to a further increased asymmetry in the processing of gravitational input, while head inclination in the opposite direction (i.e. a CW head tilt) would lead to reduced asymmetry in the gravity vector. However, the present results rather favor the conclusion that neglect patients use different information as a reference for their spatial judgments. Neglect patients seem to rely mainly on their idiotropic vector, or more specifically, their head-vertical axis. They display a tendency to orient verticality judgments towards their head z-axis, leading them to set their subjective vertical toward this axis in the conditions where the head is tilted (A-effect). Since the trunk always remained vertical in the present experiment, the orientation-specific effect is attributable to head orientation alone. This is in line with findings by Kerkhoff and Schindler (1997) indicating that variations in head orientation independently affect spatial performance in neglect patients.

Another, but similar, model which has been suggested by Luyat et al. (2001, 2002), assumes that spatial orientations are mapped in a *subjective* gravitational reference frame. The authors argue that tilted subjects do not have access to a 'veridical' gravitational reference frame, but rather to a subjective reference frame which is not congruent with the physical one. However, in healthy subjects, the *subjective* gravitational reference frame is at least congruent with the physical one in upright posture. Also, even in tilted posture, healthy subjects can still use gravitational information to counteract the attraction of the subjective vertical by the idiotropic vector. Accordingly, the healthy subjects investigated in the present study displayed only minor and nonsystematic effects of head tilt on spatial performance. Their difference thresholds were numerically slightly larger with lateral head tilt compared to upright head orientation, while there was no such effect on the constant errors. By contrast, in neglect patients, the *subjective* gravitational reference frame is *not* congruent with the physical one in upright posture. Furthermore, they cannot rely on gravitational information (as it is biased) to counteract the attraction of the subjective vertical by the idiotropic vector. Therefore, neglect patients display an increased A-effect, that is, in the case of head tilt their subjective vertical is attracted by the idiotropic vector to a much greater degree compared to healthy subjects or control patients without neglect. This means that the direction of tilt, which is mirrored by the constant errors, varies as a function of head orientation condition. Our finding of an abnormally large A-effect in patients with neglect is in line with previous studies showing similar results in patients with impaired or absent vestibular function (e.g., Bronstein et al., 1996) and support the view that this particular tilt-mediated effect is somatosensory in origin (Yardley, 1990). Somatosensory information about the orientation of the head and body in space contributes to the idiotropic vector. Since neglect patients display impaired processing of vestibular information and, thus, cannot rely on a gravitational reference frame, they have to rely on somatosensory information to a greater degree than healthy subjects.

Clinical consequences of impaired spatial orientation constancy in neglect

The present findings, showing a strong influence of head inclination in the frontal plane induced by head inclination of +/-25°, combined with previous findings, showing a significant modulation of spatial orientation performance in the lateral plane (z-plane, Schindler & Kerkhoff, 1997) and a modulation of spatial orientation in supine versus upright body position (Funk et al., 2010; Saj et al., 2005), imply a loss of *spatial orientation constancy* in patients with neglect. In other words, perception of the subjective vertical or horizontal in the visual and tactile modality changes dramatically with every change in head- or body-position in neglect patients, but not so in control patients or healthy subjects. This loss of spatial orientation constancy is multimodal and, arguably, related to the poor postural and mobility capacities characteristic for neglect patients (Lafosse et al., 2007; Pérennou, 2006; Pérennou et al., 2008). Neglect patients frequently show a very typical group of symptoms mirroring postural deficits in the frontal plane characterized by a postural imbalance caused by lateropulsion or 'pushing' behavior (Karnath, Ferber, & Dichgans, 2000), and head-/eye-position deficits in the horizontal plane characterized by marked deviations of spontaneous eye and head orientation towards the right (Fruhmann-Berger et al., 2005). Such deviations in posture, eye and head position may be understood as a pathological adjustment of the patients' 'default position', which is shifted to a new (more rightward in the frontal as well as in the horizontal plane) origin in patients with spatial neglect.

Our present results suggest that different head-positions in the frontal plane (CW or CCW head tilts) have a strong effect on visual and tactile judgments of the subjective vertical and horizontal in patients with neglect but not without neglect. Although we did not measure spontaneous head-positioning in our study, passive manipulation of head-position significantly affected verticality judgments in neglect. As it is very likely that neglect patients will change their head position spontaneously in their daily life also in the horizontal plane in both directions, for instance during transfers to bed, standing, sitting or walking, these changes in head position will inevitably also affect their judgments of verticality. We assume that the rightsided shift in spontaneous head- and eye-position described by Fruhmann-Berger et al. (2005) and the typical postural deficits in the frontal plane (Lafosse et al., 2007; Karnath et al., 2000; Pérennou, 2006; Pérennou et al., 2008) together with the pattern of results found in our study demonstrate that neglect patients show postural (including head- and eye-position) deficits in all spatial planes, which in turn affect the processing of spatial information in all spatial planes. The result of this may be an inaccurate and very instable spatial orientation - due to the pathological bias and enhanced variability of verticality judgments on the one hand and changes in verticality perception as a result of changes in head position on the other – hence an impairment in spatial orientation constancy.

Conclusion

In conclusion, the results of the present study can be taken as evidence for a supramodal spatial orientation deficit and a loss of spatial orientation constancy in neglect patients. In upright posture, spatial orientations are systematically tilted CCW in both the tactile and the visual modality. Spatial orientation judgments are furthermore systematically modulated by lateral head inclination in neglect patients and this modulation is specific for spatial neglect and not due to unilateral brain damage in general. CCW tilts of the head result in a further increase in spatial bias, whereas CW tilts of the head lead to a decrease in CCW spatial bias and thus a trend towards normal performance. This pattern of results corresponds to an increased A-effect, which can be explained by a stronger attraction of the subjective vertical by the idiotropic vector, due to impaired processing of gravitational information.

Acknowledgements

This work was supported by a Deutsche Forschungsgemeinschaft (DFG) grant to Peter Bublak, Kathrin Finke, and Georg Kerkhoff (project FOR 480, BU 1327/2-1) and to Georg Kerkhoff (IRTG 1457 "Adaptive minds").

2.2.6. References

Andersen, R.A., Essick, G.K., & Siegel, R.M. (1985). The encoding of spatial location by posterior parietal neurones. *Science, 230,* 456-458.

Andersen, R.A., & Mountcastle, V.B. (1983). The influence of the angle of gaze upon the excitability of the light sensitive neurons of the posterior parietal cortex. *Journal of Neuroscience, 3,* 532-548.

Bender, M., & Jung, R. (1948). Abweichungen der subjektiven optischen Vertikalen und Horizontalen bei Gesunden und Hirnverletzten. *European Archives of Psychiatry and Clinical Neuroscience, 181,* 193-212.

Benton, A., Hannay, H.J., & Varney, N.R. (1975). Visual perception of line direction in patients with unilateral brain disease. *Neurology, 25,* 907-910.

Bisiach, E., Capitani, E., Luzatti, C., & Perani, D. (1981). Brain and conscious representation of outside reality. *Neuropsychologia, 19*, 543-551.

Bisiach, E., & Luzatti, C. (1978). Unilateral neglect of representational space. *Cortex, 14*, 129-133.

Bisiach, E., Pizzamiglio, L., Nico, D., & Antonucci, G. (1996). Beyond unilateral neglect. *Brain, 119*, 851-857.

Brandt, Th., Dieterich, M., & Danek, A. (1994). Vestibular Cortex Lesions Affect the Perception of Verticality. *Annals of Neurology, 35*, 403-412.

Bremmer, F., Klam, F., Duhamel, J.-R., Ben Hamed, S., & Graf, W. (2002). Visual-vestibular interactive responses in the macaque ventral intraparietal area (VIP). *European Journal of Neuroscience, 16,* 1569-1586.

Bronstein, A.M., Yardley, L., Moore, A.P., & Cleeves, L. (1996). Visually and posturally mediated tilt illusions in Parkinson's disease and in labyrinthine defective subjects. *Neurology, 47,* 651-656.

Brotchie, P.R., Andersen, R.A., Snyder, L.H., & Goodman, S.J. (1995). Head position signals used by parietal neurones to encode locations of visual stimuli. *Nature, 375,* 232-235.

Cramon, D. von, & Kerkhoff, G. (1993). On the cerebral organization of elementary visuo-spatial perception. In B. Gulays, D. Ottoson, P. Roland (Eds), *Functional organisation of the human visual cortex* (pp 211-231). Oxford: Pergamon.

Day, R. H., & Wade, N. J. (1969). Mechanisms involved in visual orientation constancy. *Psychological Bulletin, 1,* 33-42.

De Renzi, E. (1982). *Disorders of space exploration and cognition.* Wiley, New York.

De Renzi, E., Faglioni, P., & Scotti, G. (1971). Judgment of spatial orientation in patients with focal brain damage. *Journal of Neurology, Neurosurgery, and Psychiatry, 34*, 489-495.

Dichgans, J., Diener, H. C., & Brandt, T. (1974). Optokinetic–graviceptive interaction in different head positions. *Acta Otolaryngologica, 78,* 213-221.

Diener, H.C., & Dichgans, J. (1988). On the role of vestibular, visual, and somatosensory information for dynamic postural control humans. *Progress in Brain Research,76,* 253–262.

Dilorenzo, J. R., & Rock, I. (1982). The rod and frame effect as a function of the righting of the frame. *Journal of Experimental Psychology: Human Perception & Performance, 8,* 536-546.

Duhamel, J.R., Colby, C.L., & Goldberg, M.E. (1998). Ventral intra-parietal area of the macaque: congruent visual and somatic response properties. *Journal of Neurophysiology, 79*, 126-136.

Engen, T. (1971). Psychophysics I: Discrimination and detection. In: Kling, J.W., & Riggs, L. (Eds). Woodworth & Schlossberg's experimental psychology (pp11-86). London: Methuen & Co.

Fimm, B., Willmes, K., & Spijkers, W. (2006). The effect of low arousal on visuo-spatial attention. *Neuropsychologia, 44*, 1261-1268.

Fruhmann-Berger, M., & Karnath, H.-O. (2005). Spontaneous eye and hand position in patients with spatial neglect. *Journal of Neurology, 252(10),* 1194-2000.

Funk, J., Finke, K., Mueller, H.J., Preger, R., & Kerkhoff, G. (2010). Systematic biases in the tactile perception of the subjective vertical in patients with unilateral neglect, and the influence of upright vs. supine posture. *Neuropsychologia, 48(1),* 298-308.

Gainotti, G., Tiacci, C. (1971). The relationships between disorders of visual perception and unilateral spatial neglect. *Neuropsychologia, 9(4),* 451-458.

Graziano, M.S.A., & Gross, C.G. (1995). The representation of extrapersonal space: A possible role for bimodal, visual-tactile neurons. In Gazzaniga, M.S. (Ed), *The Cognitive Neurosciences* (pp 1021-1034). Cambridge, MA: The MIT Press.

Grüsser, O.J., Pause, M., & Schreiter, U. (1990). Vestibular neurones in the parieto-insular cortex of monkeys (macaca fascicularis): visual and neck receptor responses. *Journal of Physiology, 430,* 559-583.

Halligan, P.W., & Marshall, J.C. (1991b). Spatial compression in visual neglect: A case study. *Cortex, 27*, 623-629.

Howard, I.P. (1982). Human visual orientation. New York: Wiley.

Howard, I. P. (1986). The perception of posture, self motion, and the visual vertical. In K. R. Boff, L. Kaufmann, & J. P. Thomas (Eds.), *Handbook of perception and human performance* (pp. 18.1-18.61). New York: Wiley.

Karnath, H.-O. (1997). Spatial orientation and the representation of space with parietal lobe lesions. *Philosophical Transactions of the Royal Society, London B, 352*, 1411 - 1419.

Karnath, H.-O., Ferber, S., & Dichgans, J. (2000). The neural representation of postural control in humans. *Proceedings of the National Academy of Sciences of the United States of America, 97(25),* 13931-13936.

Karnath, H.-O., Fetter, M., & Niemeier, M. (1998). Disentangling gravitational, environmental, and egocentric reference frames in spatial neglect. *Journal of Cognitive Neuroscience, 10*, 680–690.

Kerkhoff, G. (1999). Multimodal spatial orientation deficits in left-sided visual neglect. *Neuropsychologia, 37*, 1387-1405.

Kerkhoff, G. (2001). Spatial hemineglect in humans. Progress in Neurobiology, 63, 1-27.

Kerkhoff, G., & Marquardt, C. (1995). VS – A new computer program for detailed offline analysis of visual-spatial perception. *Journal of Neuroscience Methods, 63,* 75-84.

Kerkhoff, G., Münßinger, U., Eberle-Strauss, G., & Stögerer, E. (1992). Rehabilitation of hemianopic alexia in patients with postgeniculate visual field disorders. *Neuropsychological Rehabilitation, 2,* 21-42.

Kerkhoff, G., & Schindler, I. (1997). Head and trunk orientation modulate visual neglect. *NeuroReport, 8(12),* 2681-2685.

Kerkhoff, G., & Zoelch, C. (1998). Disorders of visuo-spatial orientation in the frontal plane in patients with visual neglect following right or left parietal lesions. *Experimental Brain Research, 122*, 108-120.

Kim, Y., Morrow, L., Passafiume, D., & Boller, F. (1984). Visuoperceptual and visuomotor abilities an locus of lesion. *Neuropsychologia, 22,* 177-185.

Ladavas, E. (1987). Is the hemispatial deficit produced by right parietal lobe damage associated with retinal or gravitational coordinates? *Brain, 110,* 167-180.

Lafosse, C., Kerckhofs, E., Troch, M., Santens, P., & Vandenbussche, E. (2004). Graviceptive misperception of the postural vertical after right hemispheric damage. *Neuroreport,* *15(5),* 887-891.

Laplane, D., & Degos, J.D. (1983). Motor neglect. *Journal of Neurology, Neurosurgery, and Psychiatry, 46,* 152-158.

Lenz, H. (1944). Raumsinnesstörungen bei Hirnverletzungen. *Deutsche Zeitschrift für Nervenheilkunde, 157*, 22-64.

Luyat, M., Gentaz, E., Corté, T., & Guarrez, M. (2001). Reference frames and haptic perception of orientation: Body and head tilt effects on the oblique effect. *Perception & Psychophysics, 63,* 541-554.

Luyat, M., & Gentaz, E. (2002). Body tilt effect on the reproduction of orientations: studies on the visual oblique effect and subjective orientations. *Journal of Experimental Psychology: Human Perception and Performance, 28(4),* 1002-1011.

Manly, T., Dobler, V. B., Dodds, C. M., & George, M. A. (2005). Rightward shift in spatial awareness with declining alertness. *Neuropsychologia, 43*, 1721-1728.

Matthias, E., Bublak, P., Müller, H. J., Schneider, W. X., Krummenacher, J. & Finke, K. (in press). The influence of alertness on spatial and non-spatial components of visual attention. *Journal of Experimental Psychology: Human Perception and Performance*.

Milner, A.D., & Harvey, M. (1995). Distortion of size perception in visuospatial neglect. *Current Biology, 5*, 85-89.

Milner, A.D., Harvey, M., Roberts, R.C., & Forster, S.V. (1993). Line bisection errors in visual neglect: Misguided action or size distortion? *Neuropsychologia, 31(1),* 39-49.

Mittelstaedt, H. (1983a). A new solution to the problem of the subjective vertical. *Naturwissenschatften, 70,* 272-281.

Mittelstaedt, H. (1986). The subjective vertical as a function of visual and extraretinal cues. *Acta Psychologica, 63,* 63-88.

Mittelstaedt, H. (1991).The role of the otoliths in perception of the orientation of self and world to the vertical. *Zoological Journal of Physiology, 95,* 419-425.

Nichelli, P., Rinaldi, M., & Cubelli, R. (1989). Selective spatial attention and length representation in normal subjects and in patients with unilateral spatial neglect. *Brain and Cognition, 9(1),* 57-70.

Parker, D. E., Poston, R. L., & Gulledge, W. L. (1983). Spatial orientation: Visual-vestibular-somatic interaction. *Perception & Psychophysics, 33,* 139-146.

Pérennou, D. (2006). Postural disorders and spatial neglect in stroke patients: A strong association. *Restorative Neurology and Neuroscience, 24(4-6),* 319-334.

Pérennou, D., Mazibrada, G., Chauvineau, V., Greenwood, R., Rothwell, J., Gresty, M.A., & Bronstein, A.M. (2008). Lateropulsion, pushing and verticality perception in hemispheric stroke: a causal relationship? *Brain, 131,* 2401-2413.

Pizzamiglio, L., Vallar, G., & Doricchi, F. (1995). Gravity and hemineglect. *NeuroReport, 7*, 370 –371.

Rock, I. (1990). The frame of reference. In I. Rock (Ed), *The legacy of Solomon Asch* (pp 243-268). Hillsdale, New Jersey: Erlbaum.

Saj, A., Honoré, J., Davroux, J., Coello, Y., & Rousseaux, M. (2005). Effect of posture on the perception of verticality in neglect patients. *Stroke, 36*, 2203-2205.

Saj, A., Honoré, J., Bernati, T., Richard, C., & Rousseaux, M. (2008). Reducing rightward bias of subjective straight ahead in neglect patients by changes in body orientation. *Journal of Neurology, Neurosurgery, and Psychiatry, 79(9),* 991-996.

Sakata, H., Taira, M., Kusunoki, M., Murata, A., & Tanaka, Y. (1997). The parietal association cortex in depth perception and visual control of hand action. *Trends in Neuroscience, 20*, 350-357.

Snyder, L.H., Batista, A.P., & Andersen, R.A. (1997). Coding of intention in the posterior parietal cortex. *Nature, 386,* 167.

Tartaglione, A., Benton, A.L., Cocito, L., Bino, G., & Favale, E. (1981). Point localisation in patients with unilateral brain damage. *Journal of Neurology, 44,* 935-941.

Tartaglione, A., Cocito, L., Bino, G., Pizio, N., & Favale, E. (1983). Further evidence for asymmetry of point localization in normals and unilateral brain damaged patients. *Neuropsychologia, 21*, 407-412.

Taylor, A.M., & Warrington, E.K. (1973). Visual discrimination in patients with localized cerebral lesions. *Cortex, 9,* 82-84.

Wade, N. J. (1968). Visual orientation during and after lateral head, body, and trunk tilt. *Perception & Psychophysics*, *3*, 215-219.

Wade, N. J. (1969). The effect of stimulus line variations on visual orientation with head upright and tilted. *Australian Journal of Psychology*, **21**, 177-185.

Wade, N.J. (1992). The representation of orientation in vision. *Australian Journal of Psychology, 44,* 139-145.

Warrington, E.K., & James, M. (1967). Disorders of visual perception in patients with localised cerebral lesions. Neuropsychologia, 5, 253-266.

Yardley, L. (1990). Contribution of somatosensory information to perception of the visual vertical with body tilt and rotating visual field. *Perception & Psychophysics, 48(2),* 131-134.

Yelnik, A. P., Lebreton, F. O., Bonan, I. V., Colle, F., Meurin, F. A., Guichard, J. P., & Vicaut, E. (2002). Perception of verticality after recent cerebral hemispheric stroke. *Stroke*, *33*, 2247-2253.

2.3. Visual context modulates the subjective vertical in neglect: Evidence for an increased Rod-and-Frame-Effect

Funk, J., Finke, K., Mueller, H.J., Utz, K.S., & Kerkhoff, G. (2011).

Neuroscience, 173, 124-134.

2.3.1. Abstract

Patients with spatial hemi-neglect display systematic deviations of the subjective vertical. The magnitude of such deviations was shown to be modulated by internal factors mediating the perception of verticality, including head-orientation. The present study investigated whether and how spatial orientation deficits are modulated by external, contextual changes in neglect patients. In a classic rod-and-frame task, we analyzed effects of frame orientation on the subjective visual vertical (SVV) in neglect patients, control patients with left- or right-sided brain damage without neglect and healthy participants. We found that neglect patients, but not brain-damaged control patients, generally display a systematic counterclockwise (CCW) tilt in their SVV judgments. Furthermore, all participant groups displayed a typical rod-and-frame effect (RFE), i.e. a modulation of the SVV as a function of frame tilt. However, in the control groups, this modulation was only moderate whereas in the neglect group SVV judgments were substantially and systematically modulated by frame orientation: with CCW frame tilts, the spatial bias of neglect patients increased as a function of the magnitude of the tilt whereas with clockwise (CW) frame tilts, the spatial bias was decreased in case of moderate frame tilts and even reversed in case of stronger frame tilts, resulting in a substantial CW spatial bias. This dramatically enhanced RFE might be caused by a pathologically increased influence of contextual cues on the subjective vertical in neglect patients as a consequence of impaired processing of gravitational information. The results indicate a systematic bias of the subjective vertical along with an impairment of spatial orientation constancy which leads to severe perturbations of subjective space as well as an increased reliance on internal and external cues mediating the perception of verticality in neglect.

Keywords: neglect, space perception, subjective vertical, RFE (rod-and-frame effect), context

2.3.2. Introduction

Brain damage, hemineglect, and tilted space

Hemispatial neglect is a supramodal neurological disorder characterized by a complex syndrome of sensory, motor and representational deficits (for a review, see Kerkhoff, 2001). Neglect patients typically fail to detect or respond to stimuli in their contralesional hemispace (Bisiach et al., 1996), show unilateral spatial representational deficits (Bisiach and Luzatti, 1978; Bisiach et al., 1981) and frequently display a reduced use of their contralesional extremities (Laplane and Degos, 1983). Although most neglect models focus on the explanation of impairments in the horizontal plane (Kerkhoff, 2001), numerous studies have demonstrated that other planes are also affected. Impairments in the frontal plane include deficits in the judgment of the subjective visual vertical (SVV) and horizontal (SVH; Howard, 1982; Lenz 1944), and judgments of oblique line orientations (Benton et al., 1975; De Renzi et al., 1971; Kim et al., 1984). Bender and Jung (1948) found that deviations of the subjective from the true vertical result from frontal or parietal (but not occipital) lobe lesions and that their direction is contralesional, with clockwise (CW) deviations following left- and counterclockwise (CCW) deviations following right-hemisphere injury. In a more recent investigation, Brandt et al. (1994) examined 71 patients with unilateral hemispheric lesions for judgment of the SVV. MRI analyses revealed that the most impaired patients had lesions centering on an area considered as the human homologue of the monkey parieto-insular-vestibular cortex (PIVC; Grüsser et al., 1990).

Interestingly, lesion sites related to deviations of the subjective vertical are neighbouring and overlapping with those known to cause the neglect syndrome, including the insula (Karnath et al., 2004), the temporo-parietal junction (e.g. Vallar and Perani, 1986), posterior parietal (e.g. Mesulam, 1999) and intraparietal cortices (Mort et al. 2003), and the superior temporal gyrus (e.g., Karnath et al., 2001, 2004) at the cortical level as well as the thalamus and basal ganglia (Vallar and Perani,1986; Karnath et al., 2004) at the subcortical level. For the perceptive/visuo-spatial component of hemineglect especially the right inferior parietal lobule seems to play a critical role (Verdon et al., 2010). Hence, it is not astonishing, that neglect patients present not only with a displacement of an egocentric reference frame to the ipsilesional side of space but also with abnormal visuo-spatial judgements, that is, CCW tilts of axes in the vertical, horizontal, and oblique orientation in the frontal plane (Kerkhoff and Zoelch, 1998). As in the horizontal plane, these deficits in the frontal plane are multimodal as they occur in both the visual and tactile modalities (with the deviation in both modalities being correlated with each other and with the neglect severity; Kerkhoff, 1999). Importantly, this multimodal deficit is not an unspecific consequence of brain damage, but seems to be specifically related to spatial neglect, as patients with left- or right-hemispheric lesions *without* neglect perform at the level of healthy control subjects (Kerkhoff, 1999). Furthermore, Yelnik et al. (2002) showed that deviations of the SVV do not primarily depend on the localization and size of the underlying lesion, but are rather related to the severity of spatial neglect. Thus, a severely disturbed representation of space in the frontal plane does not constitute an epiphenomenon, but rather a core deficit of neglect patients.

Opposing this view, there is evidence from a study of Johanssen et al. (2006) who could not find a consistent SVV bias in a group of patients with pusher syndrome and spatial neglect. However, this lack of effect in the pusher neglect patients does not necessarily invalidate the assumption that SVV deviations are a core deficit in spatial neglect since findings from research on the SVV in pusher patients are heterogeneous and there is not yet a consensus whether there is an (ipsiversive) SVV bias (Saj et al., 2005c) or no bias (Karnath et al., 2000; Johanssen et al., 2006) in such patients and how this potential bias interacts with further deficits of the patients. Interestingly, Saj et al. (2005c) found that SVV deviations were clearly clockwise in pusher neglect patients, but anticlockwise in non-pusher neglect patients. Thus, an ipsiversive bias in pusher patients for example might counteract a neglect-induced contraversive bias (note that, in the present study, no pusher patients were included in the sample of neglect patients).

Internal and external factors mediating biases in space perception in neglect

A better understanding of the factors that mediate different aspects of spatial biases in neglect patients is important for obtaining a clearer picture of the nature and the underlying mechanisms of the deficits and for identifying intervention schemes. Studies on the effectiveness of modulations of internal mediators of spatial deficits have used neck muscle vibration (e.g., Schindler et al., 2002), transcutaneous electroneural stimulation (TENS; Pizzamiglio et al., 1996), postural modulations (Karnath et al., 1998; Pizzamiglio et al., 1995), prism adaptation (e.g., Rossetti et al., 1998; Saevarsson et al., 2009; Vankilde and Habekost, 2010), and vestibular stimulation (Karnath, 1994); those on modulations of contextual factors have employed optokinetic stimulation (e.g., Mattingley et al., 1994b; Kerkhoff, 2000) and cueing (e.g., Butter and Kirsch, 1995; Lin et al., 1996). These studies enabled the development of the most applied neglect-therapies for spatially biased behavior such as, for instance, extinction, the unawareness of contralesional stimuli, or motor neglect.

More recent research has focused on the subjective vertical as a more direct measure of space perception, and examined modulations of internal mediators of verticality perception. As with other aspects of spatial bias, a number of studies have investigated the effectiveness of internal mediators of space perception. Saj et al. (2005b, 2006) demonstrated that the subjective visual vertical (SVV) in patients with right-hemispheric lesions (especially neglect patients) was significantly affected by galvanic vestibular stimulation and by postural modulations (in the fore-back dimension). We showed that the subjective *tactile* vertical

(STV), too, was significantly affected by modulations of posture in the fore-back dimension (and therefore head orientation in the saggital plane; Funk et al., 2010a). Furthermore, we found that *lateral* head tilt (head orientation in the frontal plane) had also a systematic and significant effect on the SVV in neglect patients (Funk et al., 2010b): Their CCW bias was further increased by CCW lateral head inclination, while it was substantially reduced by CW inclination. These studies demonstrate that the perception of verticality can be systematically modulated by changes in the setting of internal mediators contributing to the representation of space. However, to our knowledge, no systematic investigation of the effects of *contextual* factors, which are known to critically influence other aspects of spatial behavior (Butter and Kirsch, 1995; Lin et al., 1996; Mattingley et al., 1994b; Kerkhoff, 2000), on subjective verticality judgments in neglect has been carried out to date.

Context as a mediator of orientation perception / the rod-and-frame effect

Visual context is an important mediator of object perception and serves as a frame of reference for the apparent orientation of an object. A classical example of a context effect in the estimation of the subjective vertical is the so-called rod-and-frame effect (RFE; Asch and Witkin, 1948a, b). In rod-and-frame tasks, observers show systematic errors in setting a rod to the vertical position when it is placed inside a tilted frame compared to when it is presented without a frame or with a gravitationally vertical frame (in an otherwise dark environment, i.e., without additional contextual cues). A common interpretation of the RFE is that, in addition to gravity, the tilted frame serves as a frame of reference for the perception of the upright (e.g., Rock, 1990), that is, it acts as a world surrogate determining the apparent visual axes of space. The observers perceive rod orientation with reference to frame orientation *and* to gravity, so that the resulting rod setting usually is a compromise between the two references. At small degrees of frame tilt (up to 20°), the subjective vertical is typically tilted in the direction of the frame tilt (so-called direct effects), whereas at larger degrees, it can be tilted either in the direction of frame tilt or in the opposite direction (so-called indirect effects), depending on the symmetry axis which is used as a reference (e.g., Beh et al., 1971). The magnitude and direction of rod tilt is furthermore influenced by the size of the frame: large frames typically produce larger rod-setting errors (e.g., Ebenholtz and Callan, 1980) and only direct effects, whereas small frames can produce both direct and indirect effects, depending on the degree of frame tilt (Wenderoth and Beh, 1977).

Further research on the mechanisms underlying the RFE revealed a possible role of induced head tilt (Ebenholtz and Benzschawel, 1977; Sigman et al., 1978; 1979) and ocular torsion in the direction of the frame (e.g., Goodenough et al., 1979a). Both effects may be explained in terms of visuo-vestibular interactions. The tilted frame might produce an illusion of self-tilt in the direction opposite to that of the frame. In a compensatory manner, the rod might be set in the direction opposite to that of experienced body tilt and, thus, into the direction of frame tilt (e.g., Goodenough et al., 1979b). However, visuo-vestibular interactions alone cannot explain the variety of effects (i.e., direct and indirect effects) reported in rod-and-frame tasks; rather, purely visual mechanisms seem to be at work, too (e.g., Goodenough et al., 1979). Therefore, an alternative hypothesis of a dual-process-model has been put forward (for a review, see e.g. Spinelli et al., 1991), namely: in the case of large frames, RF phenomena are mediated by visuo-vestibular interactions; by contrast, in the case of small frames, purely visual mechanisms would be prominent.

Rationale of the present study

The objective of the present study was to investigate whether and how the systematic spatial orientation deficits in neglect patients are modulated by contextual cues. We studied the SVV in patients with right-hemispheric brain damage and left spatial neglect, patients with right- or left-hemispheric brain damage without spatial neglect (further referred to as RBD and LBD controls), and healthy control subjects in a classic rod-and-frame task. In order to systematically analyze effects of frame orientation in the different groups, participants had to vertically adjust a rod in conditions with CW or CCW frame tilts of varying magnitude (5°, 15°, or 45°).

Previous research has shown that frame tilts smaller than 20° typically produce direct effects, whereas 45° frame tilts do not cause tilt illusions (probably because the resulting figure is a symmetric diamond; e.g., Beh et al., 1971). Since healthy and also RBD and LBD control subjects can rely on both intact gravitational and contextual references, their rod settings should reflect a compromise between the objective/gravitational vertical and the orientation of the frame. Thus, we expected slight SSV tilts in the direction of frame tilt in case of a 5° or 15° CW or CCW frame tilt and no SVV tilt in case of a 45° frame tilt in these groups. By contrast, in neglect patients, the processing of gravitational information is impaired (Pizzamiglio, et al., 1995; 1997). Therefore, they cannot rely on gravitational input to the same extent and have to take into account other (e.g., contextual) information to a greater degree. This should result in an increased RFE in these patients. Since the SVV of neglect patients is already tilted CCW in general, a 5° or 15° CW tilt of the frame should lead to a reduction (or even reversal) of this pathological deviation, depending on the magnitude of the frame tilt. In contrast, a 5° or 15° CCW tilt of the frame should lead to a further increase of the deviation. A vertical (0°) frame might decrease the systematic deviation in neglect patients, as it can be used as a veridical reference for the rod setting. However, a 45° frame might either decrease the systematic error (in case it is subjectively interpreted as a symmetrical diamond) or increase the deviation (if interpreted as a CCW tilted square).

From the preceding arguments, the following hypotheses were derived: (1) Neglect patients (but not brain-damaged control patients without neglect) generally exhibit a systematic visual-spatial orientation deficit; that is, they generally display a substantial CCW tilt of their SVV. (2) Axis orientation performance is differently modulated by frame orientation in neglect patients compared to control patients and healthy controls: SVV judgments of all participants generally vary in the direction of frame tilt; however, performance of neglect patients is *far more strongly* biased compared to all control groups, since these patients are pathologically biased by contextual cues like frame tilt (as they cannot rely on gravitational information to the same extent as controls).

2.3.3. Methods

Participants

Twelve patients with right-hemispheric vascular lesions and left spatial neglect documented by clinical standard neglect tests (see below), twelve control patients with right-hemispheric and twelve control patients with left-hemispheric vascular damage without spatial neglect according to these tests (RBD or LBD controls), and twelve healthy control subjects were tested. Informed consent according to the Declaration of Helsinki II was obtained from all participants. Table 1 summarizes the demographic and clinical data of the patients. The LBD and RBD control patients were selected to match the neglect patient sample as closely as possible regarding demographic and clinical features (age, gender, aetiology, time since lesion). The mean age was 51.1 years (SD = 6.2, range = 43-63) for the neglect patients, 55.6 years (SD = 6.0, range = 46-65) for the RBD controls, 54.3 years (SD = 12.4, range = 32-71) for the LBD controls, and 47.2 years (SD = 12.7, range = 30-67) for the healthy controls. There was no significant difference with regard to age among groups (One-way ANOVA, $df=3$, $F=1.75$, $p>0.15$), nor did the gender distribution differ significantly between groups ($\Phi=0.30$, $p>0.20$). The mean time since the lesion occurred was similar in the patient groups:

5.8 months (SD = 3.7, range = 2-13) in the neglect group,5.1 months (SD = 2.6, range = 1-9) in the RBD group, and4.7 months (SD = 1.8, range = 3-9) in the LBD group (One-way ANOVA, $df=2$, $F=0.45$, $p>0.60$). Patients were only included in the sample if they had a single, vascular unilateral lesion and no evidence of a brain stem lesion (as revealed by CT/MRI). "Postural Imbalance" was rated as present in the patients when there was clinical evidence from physiotherapy or occupational therapy of a marked instability in standing and/or sitting upright and a clear preponderance of body orientation towards the ipsilesional side (see e.g. Pérennou 2006). None of the neglect patients showed contralesional pushing. All subjects were right-handed according to their verbal report.

Neglect tests

All patients underwent a screening for visual neglect on white paper (size 29.7 x 14.7 cm), including representational drawing (of a star, a daisy, a clock, a house, and a face), horizontal line bisection of a 20 x 1 cm black line, and number cancellation (10 targets in each hemispace among 100 numbers on the total page). In addition, a reading test with 180 words sensitive to neglect and hemianopic reading disturbances (Kerkhoff et al., 1992) was administered. Omissions or significant distortions of the left half of the copied figures were interpreted as an indicator of neglect. Cut-offs in the further tests were deviations of more than 5 mm from the true midpoint of a 20 cm line in line bisection, more than 1 omission in each hemispace in the number cancellation task, and more than 2 omissions or substitutions of letters or words and/or prolonged reading times (> 120 sec).

Table 1: Summary of clinical and demographic data of neglect patients, LBD and RBD control patients without neglect.

Group	Age	Sex	Etiology	Lesion	TSL months	Motor deficit	Postural Deficit	Aphasia	Visual field	Reading errors	Figure copy	Cancell. L/R	Line bisection
N+	49	1	R-MCA	P, T	12	Plegia	PI	NT	L-Quan	12	-/+	8/3	+22
N+	44	1	R-MCA	P, T	10	Paresis	PI	NT	L-Quan	8	-/+	6/4	+9
N+	43	1	R-MCA	P	5	Plegia	PI	NT	Normal	7	-/+	8/3	+7
N+	50	1	R-MCA	P, T	13	Plegia	PI	NT	Normal	8	-/+	8/5	+12
N+	48	1	R-MCA	P	5	Paresis	PI	NT	L-Quan	5	-/+	5/2	+7
N+	48	1	R-TU	P	4	Paresis	PI	NT	L-HH	5	-/+	5/1	-6
N+	52	0	R-ICB	T	3	Normal	No	NT	Normal	6	-/+	5/2	+10
N+	56	0	R-MCA	P, T	2	Plegia	PI	NT	L-Quan	11	-/+	10/3	+17
N+	63	0	R-MCA	P, T	4	Plegia	PI	NT	Normal	12	-/+	7/2	+13
N+	52	0	R-MCA	P, T	3	Paresis	PI	NT	L-Quan	10	-/+	5/2	+12
N+	47	0	R-MCA	P, T	4	Plegia	PI	NT	L-HH	37	-/+	10/5	+29
N+	61	0	R-MCA	P	4	Plegia	PI	NT	Normal	6	-/+	4/0	+7
LBD	41	1	L-MCA	F, P	9	Paresis	No	Broca	Normal	NT	+/+	0/0	-1
LBD	63	1	L-MCA	F, P	4	Paresis	No	Broca	Normal	NT	+/+	0/0	+7
LBD	56	0	L-MCA	F, T	5	Paresis	No	Amnestic	Normal	NT	+/+	0/0	-3
LBD	56	0	L-PCA	O, T	3	Normal	No	Normal	R-Quan	0	+/+	0/0	+2
LBD	64	0	L-PCA	O	3	Normal	No	Normal	Normal	1	+/+	0/0	+3
LBD	70	0	L-ICB	BG	4	Plegia	No	Broca	Normal	NT	+/+	1/0	-2
LBD	59	0	L-MCA	P, T	7	Plegia	No	Residual	R-Quan	NT	+/+	1/0	+2
LBD	38	0	L-MCA	T, P	5	Paresis	No	Residual	R-HH	NT	+/+	0/0	+5
LBD	49	1	L-MCA	T	5	Normal	No	Residual	R-Quan	NT	+/+	0/0	+4
LBD	71	1	L-TU	T, BG	3	Paresis	No	Residual	Normal	NT	+/+	0/0	0
LBD	53	0	L-TU	T	4	Normal	No	Normal	R-Quan	0	+/+	0/0	+2
LBD	32	1	L-ICB	T	4	Normal	No	NT	Normal	0	+/+	0/1	+2

Group	Age	Sex	Etiology	Lesion	TSL months	Motor deficit	Postural Deficit	Aphasia	Visual field	Reading errors	Figure copy	Cancell. L/R	Line bisection
RBD	46	0	R-MCA	P	9	Normal	No	NT	Normal	11	+/+	0/0	+2
RBD	59	0	R-ICB	T, BG	4	Paresis	No	NT	NT	1	+/+	0/1	-3
RBD	62	0	R-MCA	P, T	9	Plegia	No	NT	L-HH	0	+/+	0/0	-22
RBD	54	0	R-MCA	P, O	1	Normal	No	NT	L-HH	0	+/+	0/1	+3
RBD	55	0	R-MCA	P, T	3	Plegia	No	NT	Normal	1	+/+	0/0	-2
RBD	58	0	R-ICB	BG	4	Paresis	No	NT	Normal	0	+/+	0/0	+5
RBD	49	0	R-ICB	BG	5	Paresis	No	NT	Normal	0	+/+	0/0	+2
RBD	65	0	R-PCA	O	9	Normal	No	NT	L-HH	6	+/+	0/0	-25
RBD	59	1	R-TU	T	3	Paresis	No	NT	Normal	1	+/+	1/0	0
RBD	60	0	R-MCA	T	5	Paresis	No	NT	Normal	0	+/+	0/0	+2
RBD	53	1	R-MCA	F, BG	4	Plegia	No	NT	Normal	1	+/+	1/0	+4
RBD	47	1	R-MCA	T, F	5	Paresis	No	NT	Normal	2	+/+	1/1	+3

Abbreviations: N+, neglect patient; LBD, left brain-damaged control patient; RBD, right brain-damaged control patient; etiology: MCA/PCA, middle/posterior cerebral artery infarction; ICB, intracerebral bleeding; TU, tumor; L/R, left/right; lesion: F, frontal; P, parietal; T, temporal; O, occipital; BG, basal ganglia; postural deficit: PI, postural imbalance; No, no postural imbalance; aphasia: NT, reading not tested due to aphasia (documented by the Aachener Aphasie Test); visual field: HH, homonymous hemianopia; Quan, homonymous quadrantanopia; figure copy: performance per hemispace, −= omissions or distortions, + = normal performance; cancellation: number of omissions per hemispace; line bisection: deviation from true midline in mm to left (−) or right side (+).

Visual-spatial RFE tests

The computerized 'visual-spatial perception' program (VS; Kerkhoff and Marquardt, 1995b) was used for the measurement of the SVV. VS is based on the method of limits (Engen, 1971). In the measurement of the SVV, the experimenter manipulates the orientation of an oblique white line (18 cm x 1.4 mm) presented on a dark background in a stepwise manner until the subject indicates that it is oriented exactly vertically and then further until the subject indicates that it is no longer vertical. Based on this procedure, the psychophysical parameter 'constant error' can be calculated which denotes the difference between a participant's mean estimate (the SVV) and the true vertical and, thus, provides information about the central tendency or central error of the subject. The task was carried out either with a 20 cm x 20 cm yellow frame, presented in various orientations around the white line, or without a frame (see figure 1). There were 7 different frame conditions: (1) no frame, (2) 0° frame, (3) -5° frame, (4) +5° frame, (5) -15° frame, (6) +15° frame, and (7) 45° frame (see figure 1). Constant errors were computed directly by the software (as described above) for each subject in each frame condition. The step-width was 0.5° in all measurements. Visual-spatial measurements were taken in total darkness with the chassis of the PC-monitor, i.e., the borders of the screen, covered by an oval-shaped mask to eliminate or at least strongly reduce any visual reference cues (apart from the frame). Subjects were tested at a distance of 0.5 m from a monitor with spectacle corrections where necessary. Head position was stabilized by means of a head-and-chin rest. There were ten trials in each frame condition. Frame conditions were blocked and the sequence of blocks was counterbalanced to control for practice effects. In all conditions, starting position was 20° away from the vertical axis. The direction (CW, CCW) of the initial tilt was counterbalanced to control for effects of rotation direction. Prior to the completion of the different conditions, subjects were familiarized with the experimental setup and performed five practice trials.

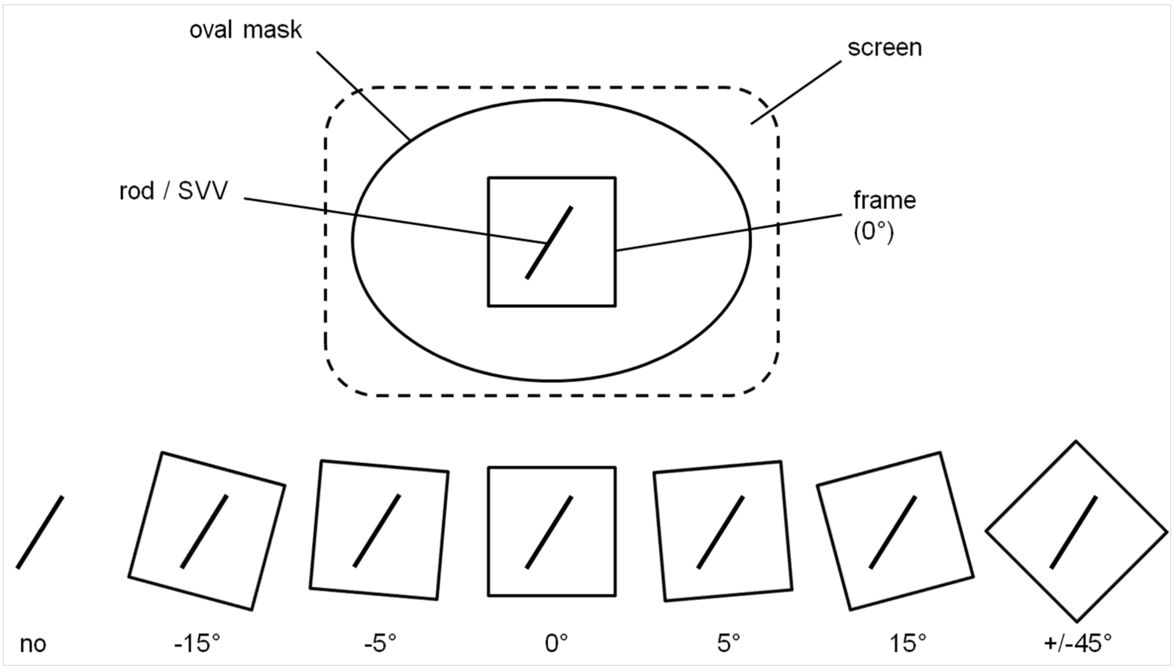

Figure 1: Experimental setup in the visual-spatial rod-and-frame task for the different frame orientation conditions (no frame, -15°, -5°, 0°, +5°, +15° and ±45°). Participants viewed only the rod and frame, the borders of the screen (dashed line) were hidden behind an oval-shaped mask to eliminate vertical/horizontal reference cues.

2.4. Statistics

Performance of the four participant groups in the baseline condition (i.e., the 'no frame' condition) was compared in a one-way ANOVA with post-hoc Scheffé tests. Furthermore, to analyze systematic deviations of the SVV from zero (the value representing the true vertical) in the baseline condition, one-sample t-tests were calculated for each participant group. To analyze the effect of context on spatial performance, a mixed-design ANOVA with the factors participant group (between-subjects factor with 4 levels: neglect patients, LBD, RBD, and healthy controls) and frame condition (within-subjects factor with 6 levels: -15°, -5°, 0°, +5°, +15°, +/-45°) was performed for the constant errors. In case of significant main effects or interactions, subsequent post-hoc comparisons were calculated: post-hoc Scheffé tests were used to compare performance between participant groups; one-way ANOVAs and contrasts (comparing each frame condition with the 0° frame condition) were used to compare performance in the different frame conditions within one subject group. Additionally, t-tests were used to compare performance between participant groups within the same frame orientation condition. The alpha-level was chosen as $p<0.05$ for all analyses, corrected for multiple comparisons.

2.3.4. Results

Neglect tests

The data of each patient in the neglect tests are given in Table 1. Neglect patients showed the characteristic pattern of asymmetrical deficits. All neglect patients showed impaired copying performance, with the typical omissions and/or distortions of the left side of the drawings. Furthermore, neglect patients displayed impaired line bisection performance: 11 out of 12 patients showed the typical rightward deviation in horizontal line bisection (mean deviation: 11.6 mm to the right, SD = 8.7). They also showed the typical pattern of omissions in the number cancellation task, with significantly more omissions in the left compared to the right hemispace [mean omissions: 6.8 in the left (SD = 2.1) and 2.7 in the right hemispace (SD = 1.5); $t(11)=10.26$, $p<0.01$] as well as impaired reading performance indicating neglect dyslexia. LBD and RBD control patients did not show such asymmetrical deficits. Rather, they showed intact drawing performance, only nonsystematic and nonsignificant deviations in line bisection performance (LBD mean: 1.8 mm to the right, SD = 2.9; RBD mean: 2.6 mm to the left, SD = 10.1) and intact number cancellation performance [LBD mean: 0.2 omissions in left (SD = 0.4) and 0.1 in right hemispace (SD = 0.3); RBD mean: 0.3 omissions in left (SD = 0.5) and 0.3 in right hemispace (SD = 0.5)]. Reading performance (not measured in 8 aphasic LBDs) was not impaired in non-aphasic LBD controls, but in 2 out of 12 RBD controls (one had hemianopic alexia due to a left-sided homonymous hemianopia).

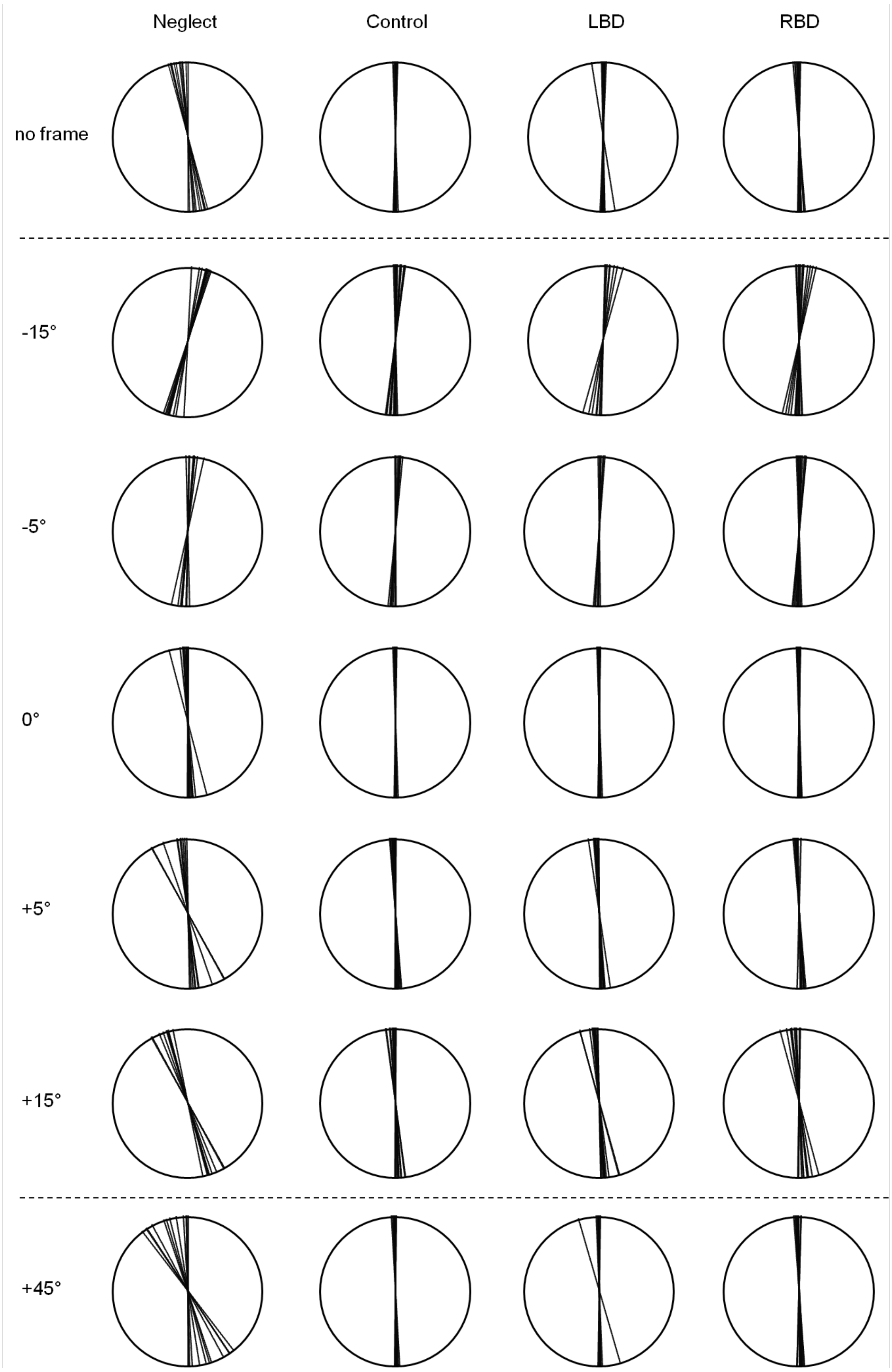

Figure 2: Performance of neglect patients, LBD and RBD control patients, and healthy controls in the visual-spatial orientation task for the six different frame orientation conditions (-15°, -5°, 0°, +5°, +15° and ±45°); the lines within the circles display the mean SVVs of individual patients and controls.

Visual-spatial orientation judgments

Figure 2 displays the visual-spatial orientation judgments of neglect patients and healthy, RBD, and LBD controls as a function of frame condition. The lines within the circles represent the mean SVVs of the individual participants. While the healthy subjects, as well as the RBD and LBD controls, show generally only minor deviations of their SSV from the true vertical, SVV judgments of neglect patients display a marked and systematic CCW tilt in the baseline condition and are furthermore substantially and systematically modulated by frame orientation. Table 2 summarizes the mean constant errors for the six different frame orientations in all subject groups.

	Healthy	**LBD**	**RBD**	**N+**
-15°	-2.7° (SD = 3.0)	-5.5° (SD = 4.2)	-3.5° (SD = 4.9)	-13.3° (SD = 4.1)
-5°	-1.6 (SD = 1.9)	-2.3° (SD = 1.6)	-1.7° (SD = 2.5)	-4.4° (SD = 3.4)
0°	0.2° (SD = 0.6)	0.2° (SD = 0.8)	0.2° (SD = 0.9)	3.0° (SD = 4.0)
5°	1.8° (SD = 1.5)	2.8° (SD = 2.1)	2.4° (SD = 1.8)	12.4° (SD = 10.9)
15°	2.7° (SD = 2.5)	5.5° (SD = 4.7)	4.8° (SD = 4.4)	18.2° (SD = 5.5)
±45°	0.7° (SD = 1.0)	1.7° (SD = 4.7)	1.3° (SD = 1.6)	16.2° (SD = 13.9)

Table 2: Constant errors (and standard deviations) for the six different frame orientation conditions (-15°, -5°, 0°, +5°, +15° and ±45°) in healthy, LBD, and RBD control subjects and neglect patients (N+); positive constant errors indicate CCW tilts of the SVV, negative constant errors CW tilts.

Group differences and general direction of SVV tilt

Figure 3 displays the average constant errors of the SVV across all frame conditions and separately for the 'no frame' condition for each subject group. While the normal subjects and also the RBD and LBD controls show only marginal deviations of their SVV, neglect patients display systematically positive constant errors, indicating a marked CCW tilt of the SVV. A one-way ANOVA with post-hoc Scheffé tests for the between-group comparison of SVV judgements in the 'no frame' condition revealed a significant effect of group (df=3, F=17.66,

$p<0.01$). Performance of neglect patients differed significantly from all control groups (all $p<0.01$), while performance of the control groups was highly comparable (all $p>0.70$). Furthermore, to assess the systematic direction of tilt without contextual information, one-sample t-tests were calculated for the constant errors of each group in the 'no frame' condition. Constant errors of healthy, LBD and RBD controls did not differ significantly from zero (all $p>0.05$). By contrast, those of neglect patients were significantly larger than zero ($t(11)=5.35$; $p<0.01$). Positive constant errors indicating CCW tilts of the SVV were shown by eleven of twelve neglect patients (one did not show any tilt). That is, without additional contextual information, neglect patients displayed reliable, substantial, and systematic CCW tilts of the SVV.

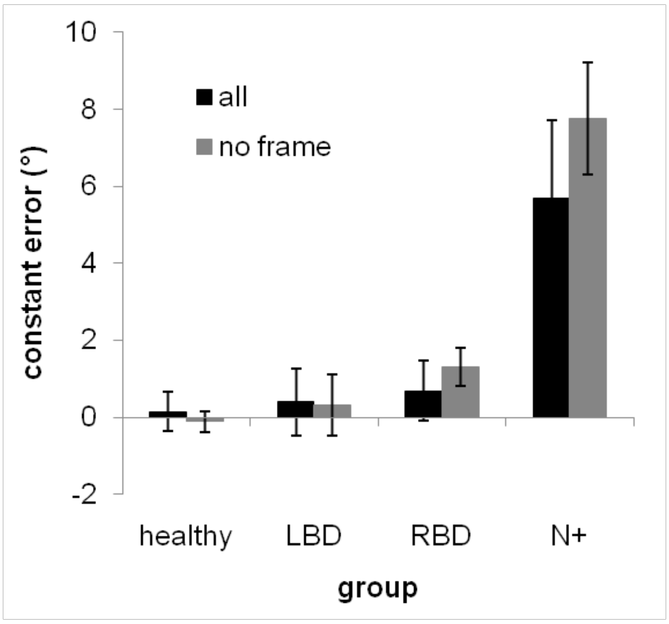

Figure 3: Constant errors (means and standard errors) in the SVV for the 'no frame' condition (grey) and across all frame conditions (black) in neglect patients (N+), healthy, LBD, and RBD control subjects; positive constant errors indicate CCW tilts of the SVV, negative constant errors CW tilts.

Effects of frame condition on SVV tilt

Figure 4 presents the average constant errors of the SVV in order to demonstrate the RFEs, separately for each frame condition and for each participant group. As can be seen, all groups showed tilts of the SSV as a function of frame condition: Only direct RFEs were obtained, that is, CW frame tilts resulted in a CW tilt of the SVV, while CCW frame tilts resulted in a CCW tilt (relative to the true vertical and relative to the SVV in the 'no frame' and in the 0° frame condition). The RFEs increased with increasing frame tilts, that is, small frame tilts led to minor changes in the SVV, whereas large frame tilts led to major changes. Moreover, Figure 4 shows that neglect patients displayed the most marked SVV modulations as a function of frame condition, that is, their SVV was tilted in the direction of frame tilt to a much larger degree than those of all three control groups.

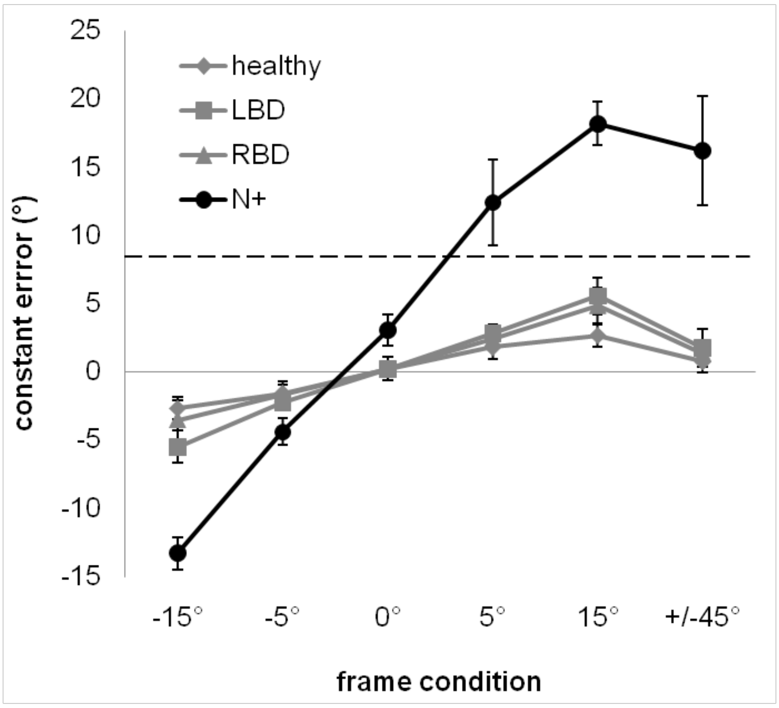

Figure 4: Constant errors (means and standard errors) in the SVV for the different frame orientation conditions (-15°, -5°, 0°, +5°, +15° and ±45°) in neglect patients (N+), healthy, LBD, and RBD control subjects; positive constant errors indicate CCW tilts of the SVV, negative constant errors indicate CW tilts; the straight line at 0° indicates the true vertical; the dashed line indicates the constant errors of neglect patients in the 'no frame' condition.

A mixed-design ANOVA (with the factors subject group and frame condition) revealed significant main effects of group (*df*=3, *F*=10.83, *p*<0.01) and frame condition (*df*=5, *F*=71.60, *p*<0.01), and a significant interaction of group and frame condition (*df*=15, *F*=15.54, *p*<0.01). Neglect patients generally displayed significantly larger constant errors compared to all control groups (all *p*<0.01), whereas the performance of healthy, RBD and LBD controls was highly comparable (all *p*>0.95, n.s.).

One-way ANOVAs revealed that frame tilt significantly affected performance in all subject groups, i.e. in neglect patients (*df*=5, *F*=37.20*,* *p*<0.01), RBD (*df*=5, *F*=10.92*,* *p*<0.01), LBD (*df*=5, *F*=16.74*,* *p*<0.01), and healthy controls (*df*=5, *F*=12.78*,* *p*<0.01). In all subjects, a 5° or 15° CW or CCW frame tilt resulted in a significant SVV tilt in the same direction (all *p*>0.05) compared to the 0° frame condition and SVV tilts were generally larger with increasing frame tilt (see figure 4). The 45° frame did not cause any SVV tilt in healthy, RBD and LBD controls (all *p*>0.05), but a strong CCW tilt of the SVV in neglect patients (*p*<0.01). Furthermore, the direct RFEs were much larger in the neglect patients compared to all other subject groups. Additional t-tests revealed that neglect patients showed a significantly larger CCW tilt of the SVV compared to all control groups in the +5°, +15° and +45° frame conditions (all *p*<0.05) and a significantly larger CW tilt in the -15° frame condition. Performance in the -5° and the 0° frame condition did not differ significantly between neglect patients and control groups after α-correction (all *p*>0.05). Performance between the three control groups did not differ significantly in any frame condition (all *p*>0.05).

2.3.5. Discussion

The rationale of the present study was to investigate the modulation of spatial orientation judgments by visual contextual cues in neglect. Visual-spatial axis orientation performance in a classic rod-and-frame task was analyzed in patients with right hemispheric lesions and left spatial neglect, LBD and RBD control patients without neglect, and healthy control subjects. Our hypotheses were that neglect patients would display a systematic CCW bias in the SSV and that, furthermore, axis orientation judgments would be modulated by frame orientation to a markedly larger degree in neglect patients compared to control groups.

As expected, neglect patients generally showed a systematic and significant CCW tilt in their SVV in the classical, reference condition without frame. Although the oval mask could serve as visual context information also in the condition 'no frame', it provides, if any, only vague cues about the cardinal axes indicating the horizontal and vertical orientation. Therefore, the CCW tilt in neglect patients in the present study unlikely represents a bias that is associated with this visual reference. The results in the ‘no frame’ condition replicate findings of previous studies in the field: they show the typical pattern of bias which has already been demonstrated in several studies in the visual domain with (Kerkhoff & Zoelch, 1998; Kerkhoff 1999) and without an oval shaped mask (Saj et al., 2005b; Yelnik et al., 2002) as well as in the tactile domain (i.e., also without a mask; Kerkhoff, 1999). Interestingly, a vertically aligned frame (0° frame) reduced this bias significantly compared to the ‘no frame’ condition, presumably because it provided a strong orthogonal, external reference for the setting of the vertical.

In all four subject groups, axis orientation performance was significantly and systematically modulated by frame tilt. The RFEs were generally direct, that is, the SVV was biased *in direction of frame tilt*. In line with previous research (e.g., Beh et al., 1971), the control groups showed only slight, but consistent direct effects in case of small, 5° or 15°, CW or CCW frame tilts and no SVV tilt in case of a 45° frame tilt. In neglect patients, the effect of frame orientation was dramatically increased, that is, the magnitude of the direct RFE was approximately three times as large in these patients as in the controls. Since the SVV of neglect patients was already tilted CCW in the ‘no frame’ and also in the 0° frame condition, a CCW tilt of the frame led to a further increase of the subjective bias. By contrast, a CW tilt of the frame led not simply to a reduction, but rather to a reversal of the bias, that is: a CW tilt of the SSV.

An exceptional case was the 45° frame condition: a 45° frame did not bias performance in the healthy, LBD, and RBD control groups, presumably because it can be used efficiently as a helpful reference cue (as the edges of a 45° frame point to the top and the bottom and the frame actually represents a symmetrical diamond; Beh et al., 1971). In neglect patients, by contrast, a 45° frame caused a marked bias, that is, it increased the CCW bias by an amount comparable to the 15 ° frame. This pattern indicates that neglect patients are not only unable to use the symmetrical contextual information provided by the diamond efficiently; rather, they seem to interpret this frame as a square tilted CCW, leading to a large direct RFE, that is, a large CCW tilt of the SVV. Thus, the 45°-diamond-shaped frame deteriorated the already impaired task performance *selectively* in the neglect group, while it permitted almost normal performance in all other groups (Fig. 4).

Differential effects of contextual modulations on the SVV

Previous research has shown that different reference frames can be selected to define a visual orientation in space (for reviews, see, e.g., Howard, 1982, Rock, 1990; Wade, 1992). Among the egocentric and allocentric reference frames in which spatial orientations can be mapped, most important for the judgment of the subjective visual vertical are probably the gravitational as well as the visual reference frame. Visual, gravitational, and also other (e.g., somatosensory) information is integrated in the intraparietal cortex to generate a subjective percept of space (e.g., Bremmer et al., 2002; Duhamel et al., 1998). If information from different sources is congruent, that is, if the different frames of reference are aligned, the subjective perception of an orientation corresponds to the ‘veridical’ orientation. However, even in participants without disturbed spatial information perception, the information delivered from different sources can be incongruent in certain conditions, as it is the case, for example, in the classic rod-and-frame task. Here, in addition to gravity, the tilted frame serves as a frame of reference for the perception of the upright, that is, it acts as a world surrogate that determines the apparent visual axes of space (e.g., Rock, 1990). The orientation of the rod is consequently perceived with reference to frame orientation *and* to gravity, so that the resulting rod setting usually is a compromise between the two references. This is exactly the behavior found in healthy, LBD, and RBD controls in the present study. They showed systematic, but only moderate deviations of the SVV (<3° for the ±5° frame condition and <6° for the ±15° frame condition) in the direction of the frame. This pattern of results indicates that frame orientation serves as a frame of reference to a certain extent and therefore biases the rod settings in the control subjects. However, visual information about the orientation of the frame is integrated with intact gravitational information, which is used as a reference for the perception of the upright, too, and thus reduces the effect of frame orientation on the SVV.

By contrast, in neglect patients, the processing of gravitational input is impaired (i.e., asymmetric) and gravitational information cannot be used as an 'intrinsic' reference for the perception of the upright to the same extent as in healthy subjects. This is most probably the reason why neglect patients showed such a strong impact of visual contextual information on the SVV. In these patients, the SVV deviations were as large or even larger than the angles of frame orientation tilt (-13.3° and -4.4° deviation in the -15° and -5° frame conditions and 12.4° and 18.2° deviation in the 5° and 15° frame conditions). Larger CCW deviations in comparison to CW deviations can be explained by a general CCW tilt of the SVV of neglect patients. The increased impact of visual contextual information on the SVV in neglect patients is in line with previous findings of enhanced effects of modulations of internal mediators of verticality perception, such as head orientation (Funk et al., 2010b). However, a new and particularly interesting finding of the present study is the reversed bias of the SVV in neglect patients in case of CW frame tilt. In general, the 'default mode' of neglect patients is a systematic and substantial CCW bias of the SVV. Previous research (e.g., Funk et al., 2010b; Saj et al., 2006) has demonstrated that this CCW bias can be increased or decreased by modulators of verticality perception. However, to our knowledge, a strong reversal of the spatial bias in neglect patients by visual contextual information as it is revealed here has not been shown thus far. It appears that the spatial performance of neglect patients is not only instable with regard to the magnitude of the pathological bias, but also with respect to its polarity, which is in line with the view that neglect patients are characterized by a loss of spatial orientation constancy. That is, neglect patients display both a consistent CCW tilt of the SVV and a loss of its constancy, which leads to systematic deviations of subjective space as well as an increased reliance on internal and external cues mediating the perception of verticality. The systematic deviations of subjective space are observable under specific (postural) circumstances - in an upright posture with a vertical head position. With lateral head inclination (Funk et al., 2010b), in supine body position (Saj et al., 2005b) or with certain types of visual context (the present paper), the tilt might change, i.e. be reduced or even reversed.

We suggest that the strong modulations of space/verticality perception in neglect patients might depend upon a central mechanism related to multisensory integration and space representation in intraparietal cortical areas. This idea has for example already been put forward by Rosetti et al., (1998), who reported a larger prism adaptation after-effect in neglect patients compared to controls. Generally, it appears that the performance of neglect patients in various spatial tests, including the SVV, is influenced more than the one of other brain-damaged patients or healthy controls by many internal (e.g., prism adaptation, neck muscle vibration, vestibular stimulation) and external (e.g., visual or auditory cues) cues mediating space representation. This abnormal weighting of cues mediating space/verticality perception might be the consequence of an impaired integration of multimodal information in the parietal cortex due to a pathological processing of graviceptive information.

Clinical and daily-life consequences of impaired spatial orientation constancy

It is likely that this effect – the loss of spatial orientation constancy and the pathologically increased influence of contextual visual information – has profound consequences in daily life. It can be conjectured that neglect patients have great difficulties in estimating verticality in the presence of additional oblique contours visible in the environment. A typical situation or scene in the daily routine, which contains multiple complex stimuli (and, therefore, also orientations), provides many different sources of context information. It would, thus, to be expected that the perception of such complex visual stimulation will lead to similar biases or even greatly increase the biases observed with the experimentally reduced stimulation in the present study. That is, depending on the predominant contextual information, different orientation biases could result which would in turn continuously change through egomotion or moving scenes/stimuli.

In this context it is worth mentioning that the size of the perceptual tilt of the SSV in the rod-and-frame test was found to predict poor ambulation performance in patients with left hemiplegia (Bruell et al, 1957, 1958; note that, unfortunately, these reports did not mention explicitly whether their patients had left-sided visual neglect). Also, the notable deficits in drawing and copying performance that neglect patients typically display could conceivably stem from (or at least be increased by) given or already drawn orientations that impede the correct drawing of new orientations. The inaccurate and very instable representation of spatial orientations changing rapidly with changes in external visual and internal modulations might therefore profoundly affect performance in clinical tests as well as fundamental competencies indispensable for managing daily life (e.g., ambulation performance).

In the present study, we showed that context information can increase, reduce, or reverse the orientation bias in neglect patients (depending on the frame orientation). Thus, visual contextual information seems to be a good candidate to manipulate this bias and could therefore be possibly used as one component of neglect therapy. Further research is necessary to investigate whether, in therapy, certain types of contextual information (e.g., a visually tilted chamber) might induce positive and desirably also long-lasting effects on orientation performance in neglect patients.

Limitations of the study

The present results, together with findings from other studies in the field, indicate a functional relation between spatial neglect and a CCW bias of the SVV. The neuropsychological methodology used in this study has inherent limitations which concern the conclusion that SVV tilts are a core deficit in spatial neglect rather than a highly correlated epiphenomenon. The high comorbidity along with the correlation between neglect severity and the magnitude of SVV tilt serve as evidence for the former assumption, which is advocated in the present study. However, if neglect is caused by lesions close to structures that are responsible for SVV deviations, we cannot exclude a high comorbidity without a direct functional relationship. In this case, not the presence or absence of spatial neglect, but the exact brain area affected would be crucial for the presence and magnitude of SVV bias. The topographical accuracy of neuropsychological studies based on the individual lesions would be a critical point with regard to this question. Unfortunately, the structural images of the patients' lesions cannot be provided in this paper. Nevertheless, the present study is the first to demonstrate that neglect patients - included on the basis of descriptions of the lesion sites and the presence of the syndrome assessed via behavioral tests - suffer from a spatial deficit which can be significantly modulated by changes in contextual visual information.

Conclusion

When combining the present finding of a strong influence of *contextual* visual information on the subjective vertical with previous findings indicating a significant impact of modulations of *internal* mediators of verticality perception (e.g., lateral head orientation: Funk et al., 2010b; and posture: Funk et al., 2010a; Saj et al, 2005b), the emerging picture is one of a loss (or an impairment) of *spatial orientation constancy* in patients with neglect. This impairment of spatial orientation constancy along with a systematic bias of the subjective vertical leads to severe perturbations of subjective space as well as an increased reliance on internal and external cues mediating the perception of verticality in neglect. Put differently: in neglect patients, the (already perturbed) perception of the subjective vertical changes dramatically not only with changes in head- or body-position, but also with modifications of contextual visual information that serve as a reference for the perception of spatial orientation. Modulations of internal and external cues mediating the perception of space do affect orientation performance also in healthy subjects or brain-damaged patients without neglect. However, in neglect patients, this modulation is pathologically exacerbated, since they are not able to use intact gravitational information as a reference for the perception of the upright to accurately integrate and counterbalance other sources of input. The result of this may be an inaccurate and very instable representation of spatial orientations changing rapidly with manipulations of internal and/or external modulators of subjective space perception, which has profound consequences in daily life of neglect patients.

Acknowledgements

This work was supported by a Deutsche Forschungsgemeinschaft (DFG) grant to Peter Bublak, Kathrin Finke, and Georg Kerkhoff (project FOR 480, BU 1327/2-1) and to Georg Kerkhoff (IRTG 1457 “Adaptive minds”).

2.3.6. References

Asch, S.E., & Witkin, H.A. (1948a). Studies in space orientation: I. Perception of the upright with displaced visual fields. *Journal of Experimental Psychology, 38,* 325-337.

Asch, S.E., & Witkin, H.A. (1948b). Studies in space orientation: II. Perception of the upright with displaced visual fields and with body tilted. *Journal of Experimental Psychology, 38,* 455-477.

Beh, H.C., Wenderoth, P.M., & Purcell, A.T. (1971). The angular function of a rod-and-frame illusion. *Perception & Psychophysics, 9(4),* 353-355.

Bender, M., & Jung, R. (1948). Abweichungen der subjektiven optischen Vertikalen und Horizontalen bei Gesunden und Hirnverletzten. *European Archives of Psychiatry and Clinical Neuroscience, 181,* 193-212.

Benton, A., Hannay, H.J., & Varney, N.R. (1975). Visual perception of line direction in patients with unilateral brain disease. *Neurology, 25,* 907-910.

Bisiach, E., Capitani, E., Luzatti, C., & Perani, D. (1981). Brain and conscious representation of outside reality. *Neuropsychologia, 19(4),* 543-551.

Bisiach, E., & Luzatti, C. (1978). Unilateral neglect of representational space. *Cortex, 14,* 129-133.

Bisiach, E., Pizzamiglio, L., Nico, D., & Antonucci, G. (1996). Beyond unilateral neglect. *Brain, 119,* 851-857.

Brandt, T., Dieterich, M., Danek, A. (1994). Vestibular Cortex Lesions Affect the Perception of Verticality. *Annals of Neurology, 35,* 403-412.

Bremmer, F., Klam, F., Duhamel, J.R., Ben Hamed, S., & Graf, W. (2002). Visual-vestibular interactive responses in the macaque ventral intraparietal area (VIP). *European Journal of Neuroscience, 16,* 1569-1586.

Bruell, J.H., & Peszczynski, M. (1958). Perception of verticality in hemiplegic patients in relation to rehabilitation. *Clinical Ophthalmology, 12,* 124-130.

Bruell, J.H., Peszczynski, M., & Volk, D. (1957). Disturbance of perception of verticality in patients with hemiplegia: second report. *Archives of Physical Medicine and Rehabilitation, 38,* 776-780.

Butter, C.M., & Kirsch, N. (1995). Effect of lateralized kinetic visual cues on visual search in patients with unilateral spatial neglect. *Journal of Clinical and Experimental Neuropsychology, 17,* 856-867.

De Renzi, E., Faglioni, P., & Scotti, G. (1971). Judgment of spatial orientation in patients with focal brain damage. *Journal of Neurology, Neurosurgery, and Psychiatry, 34,* 489-495.

Duhamel, J.R., Colby, C.L., & Goldberg, M.E. (1998). Ventral intra-parietal area of the macaque: congruent visual and somatic response properties. *Journal of Neurophysiology, 79,* 126-136.

Ebenholtz, S.M., & Benzschawel, T.L. (1977). The rod and frame effect and induced head tilt as a function of observation distance. *Perception & Psychophysics, 13,* 491-496.

Ebenholtz, S.M., & Callan, J.W. (1980). Modulation of the rod and frame effect: Retinal angle vs apparent size. *Psychological Research, 42(4),* 327-334.

Engen, T. (1971). Psychophysics I: Discrimination and detection. In: *Woodworth & Schlossberg's experimental psychology* (J.W. Kling & L. Riggs, Eds), pp11-86. London: Methuen & Co.

Funk, J., Finke, K., Mueller, H.J., Preger, R., & Kerkhoff, G. (2010a). Systematic biases in the tactile perception of the subjective vertical in patients with unilateral neglect, and the influence of upright vs. supine posture. *Neuropsychologia, 48(1),* 298-308.

Funk, J., Finke, K., Mueller, H.J., Utz, K.S., & Kerkhoff, G. (2010b). Effects of lateral head inclination on multimodal spatial orientation judgments in neglect: Evidence for impaired spatial orientation constancy. *Neuropsychologia, 48(6),* 1616-1627.

Goodenough, D.R., Oltman, P.K., Sigman, E., Rosso, J., & Mertz, H. (1979b). Orientation contrast effects in the rod-and-frame test. *Perception & Psychophysics, 25(5),* 419-424.

Goodenough, D.R., Sigman, E., Oltman, P.K., Rosso, J., & Mertz, H. (1979a). Eye torsion in response to a tilted visual stimulus. *Vision Research, 19(10),* 1177-1179.

Grüsser, O.J., Pause, M., & Schreiter, U. (1990). Vestibular neurones in the parieto-insular cortex of monkeys (macaca fascicularis): visual and neck receptor responses. *Journal of Physiology, 430,* 559-583.

Howard, I.P. (1982). *Human visual orientation.* New York: Wiley.

Johannsen, L., Fruhmann-Berger, M., & Karnath, H.O. (2006). Subjective visual vertical (SVV) determined in a representative sample of 15 patients with pusher syndrome. *Journal of Neurology, 253,* 1367-1369.

Karnath, H.O. (1994). Subjective body orientation in neglect and the interactive contribution of neck muscle proprioceptive and vestibular stimulation. *Brain, 117,* 1001-1012.

Karnath, H.O., Ferber, S., & Dichgans, J. (2000). The origin of contraversive pushing.

Neurology, 55, 1298-1304.

Karnath, H.O., Fetter, M., & Niemeier, M. (1998). Disentangling gravitational, environmental, and egocentric reference frames in spatial neglect. *Journal of Cognitive Neuroscience, 10,* 680–690.

Kerkhoff, G. (1999). Multimodal spatial orientation deficits in left-sided visual neglect. *Neuropsychologia, 37(12),* 1387-1405.

Kerkhoff, G. (2000). Multiple perceptual distortions and their modulation in patients with left visual neglect. *Neuropsychologia, 38(7),* 1073-86.

Kerkhoff, G. (2001). Spatial hemineglect in humans. *Progress in Neurobiology, 63,* 1-27.

Kerkhoff, G., & Marquardt, C. (1995). VS – A new computer program for detailed offline analysis of visual-spatial perception. *Journal of Neuroscience Methods, 63,* 75-84.

Kerkhoff, G., Münßinger, U., Eberle-Strauss, G., & Stögerer, E. (1992). Rehabilitation of hemianopic alexia in patients with postgeniculate visual field disorders. *Neuropsychological Rehabilitation, 2,* 21-42.

Kerkhoff, G., & Zoelch, C. (1998). Disorders of visuo-spatial orientation in the frontal plane in patients with visual neglect following right or left parietal lesions. *Experimental Brain Research, 122,* 108-120.

Kim, Y., Morrow, L., Passafiume, D., & Boller, F. (1984). Visuoperceptual and visuomotor abilities an locus of lesion. *Neuropsychologia, 22(2),* 177-185.

Laplane, D., & Degos, J.D. (1983). Motor neglect. *Journal of Neurology, Neurosurgery, and Psychiatry, 46,* 152-158.

Lenz, H. (1944). Raumsinnesstörungen bei Hirnverletzungen. *Deutsche Zeitschrift für Nervenheilkunde, 157,* 22-64.

Lin, K.C., Cermak, S.A., Kinsbourne, M., & Trombly, C.A. (1996). Effects of left-sided movements on line bisection in unilateral neglect. *Journal of the International Neuropsychological Society, 2,* 404-411.

Mattingley, J.B., Bradshaw, J.L., & Bradshaw, J.A. (1994). Horizontal visual motion modulates focal attention in left unilateral spatial neglect. *Journal of Neurology, Neurosurgery, and Psychiatry 57,* 1228-1235.

Pizzamiglio, L., Vallar, G., & Doricchi, F. (1995). Gravity and hemineglect. *Neuroreport, 7,* 370 –371.

Pizzamiglio, L., Vallar, G., & Doricchi, F. (1997). Gravitational inputs modulate visuospatial neglect. *Experimental Brain Research, 117,* 341-345.

Pizzamiglio, L., Vallar, G., & Magnotti, L. (1996). Transcutaneous electrical-stimulation of the neck muscles and hemineglect rehabilitation. *Restorative Neurology and Neuroscience, 10,* 197-203.

Rock, I. (1990). The frame of reference. In: *The legacy of Solomon Asch* (I. Rock, Ed), pp 243-268. Hillsdale, New Jersey: Erlbaum.

Rossetti, Y., Rode, G., Pisella, L., Farné, A., Boisson, D., & Perenin, M.T. (1998). Prism adaptation to a rightward optical deviation rehabilitates left hemispatial neglect. *Nature, 98,* 166-169.

Saevarsson, S., Kristjánsson, Á., Hildebrandt, H., & Halsband, U. (2009). Prism adaptation improves visual search in hemispatial neglect. *Neuropsychologia, 47(3),* 717-725.

Saj, A., Honoré, J., Coello, Y., & Rousseaux, M. (2005). The visual vertical in the pusher syndrome: Influence of hemispace and body position. *Journal of Neurology, 252,* 1367-1369.

Saj, A., Honoré, J., Davroux, J., Coello, Y., & Rousseaux, M. (2005). Effect of posture on the perception of verticality in neglect patients. *Stroke, 36,* 2203-2205.

Saj, A., Honoré, J., & Rousseaux, M. (2006). Perception of the vertical in patients with right hemispheric lesion: Effect of galvanic vestibular stimulation. *Neuropsychologia, 44,* 1509-1512.

Schindler, I., Kerkhoff, G., Karnath, H.O., Keller, I., & Goldenberg, G. (2002). Neck muscle vibration induces lasting recovery in spatial neglect. *Journal of Neurology, Neurosurgery, and Psychiatry, 73,* 412-419.

Sigman, E., Goodenough, D.R., & Flanagan, M. (1978). Subjective estimates of body tilt and the rod-and-frame test. *Perceptual and Motor Skills, 47,* 1051-1056.

Sigman, E., Goodenough, D.R., & Flanagan, M. (1979). Instructions, illusory self-tilt, and the rod-and-frame test. *Quarterly Journal of Experimental Psychology, 31,* 155-165.

Spinelli, D., Antonucci, G., Goodenough, D.R., Pizzamiglio, L., & Zoccolotti, P. (1991). Psychophysiological mechanisms underlying the rod and frame illusion. In: *Field dependence-independence: Cognitive style across the life span* (S. Wapner & J. Demick, Eds), pp. 37-60. Hillsdale, New Jersey: Erlbaum.

Vallar, G., & Perani, D. (1986). The anatomy of unilateral neglect after right hemisphere stroke lesions. A clinical/CT-scan correlation study in man. *Neuropsychologia, 24,* 609-622.

Vangkilde, S., & Habekost, T. (2010). Finding Wally: Prism adaptation improves visual search in chronic neglect. *Neuropsychologia, 48,* 1994-2004.

Wade, N.J. (1992). The representation of orientation in vision. *Australian Journal of Psychology, 44,* 139-145.

Wenderoth, P.M., & Beh, H.C. (1977). Component analysis of orientation illusions. *Perception, 6(1),* 57-75.

Yelnik, A.P., Lebreton, F.O., Bonan, I.V., Colle, F., Meurin, F.A., Guichard, J.P., & Vicaut, E. (2002). Perception of Verticality After Recent Cerebral Hemispheric Stroke. *Stroke, 33,* 2247-2253.

2.4. Effects of feedback-based visual line orientation discrimination training in visuospatial disorders after stroke

Funk, J., Finke, K., Reinhart, S., Kardinal, M., Utz, K.S., Rosenthal, A., Kuhn, C., Müller, H.J., & Kerkhoff, G. (submitted). *Neurorehabilitation and Neural Repair.*

2.4.1. Abstract

Patients with right or more rarely left parieto-temporal lesions often show profound visuospatial and -constructive disorders which impair spatial capacities, activities of daily living (ADL) functions and long-term outcome. Early clinical studies showed improvements with systematic training of perception. Recent studies of perceptual learning in healthy subjects suggest rapid improvements in perceptual learning of spatial line orientation, with partial transfer to non-trained line orientations. The present study investigated a novel perceptual training procedure for the rehabilitation of patients with severe visuospatial deficits. 13 stroke patients showing profound deficits in line orientation and related visuospatial tasks performed a repetitive feedback-based, computerized training of visual line orientation over 11 (mean) treatment sessions. Visual line orientation discrimination and further visuospatial and –constructive tasks were assessed before and after training. We found a) rapid improvements in trained but also in non-trained spatial orientations during training in all 13 patients, partially up to a normal level, b) interocular transfer of training effects to the non-trained eye in 2 patients suggesting a central, postchiasmatic locus for this perceptual improvement, c) stability of the obtained improvements at 2-months follow-up, and d) graded transfer of improvements to related spatial tasks such as horizontal writing, analogue clock-reading and visuoconstructive capacities. In summary, our results show a considerable potential for treatment-induced improvements in visuospatial deficits following perceptual, feedback-based training of visual line orientation which might be used for a better treatment of spatially impaired stroke patients.

Keywords: parietal, line orientation, space perception, visuospatial, perceptual learning, rehabilitation

2.4.2. Introduction

Visuospatial disorders after stroke

Stroke lesions of extrastriate cortical and subcortical structures, e.g., parietal, temporo-parietal, thalamic or basal ganglia lesions of the right (50-70%), or more rarely also the left hemisphere (30-50%), lead to profound visuospatial disorders (Kaplan & Hier, 1982; Meerwaldt & Van Harskamp, 1982). Impairments in the perception of visual space as well as in acting and orienting in space affect are typically more severe and more frequent in right- compared to left-hemispheric brain damage (Kim et al., 1984). Visuospatial deficits include visual line orientation judgements (Benton et al., 1975; De Renzi et al., 1971), the subjective visual and tactile vertical (Pérennou et al., 2008), line bisection / subjective straight ahead (Ferber & Karnath, 1999), size, distance and position estimation (Tartaglione et al., 1983), clock reading / drawing (Freedman et al., 1994), and block-design performance (Young et al., 1983).

Deficits in visual orientation discrimination most frequently occur after lesions affecting the (temporo-) parietal lobe and/or the basal ganglia (Benton et al., 1975; Kim et al., 1984). Accordingly, recent patient and imaging studies support the view that the right parietal cortex plays a dominant role in orientation perception (Ng et al., 2000; Sack et al., 2001; Taira et al., 1998; Tranel et al., 2009). There is, however, also evidence that several further brain regions contribute to visual orientation discrimination, including the right putamen and the lateral occipital cortex (e.g., Vandenberghe et al., 1996).

Therapeutic approaches

Visuospatial disorders are often accompanied by substantial deficits in mobility and ADL functions and show adverse effects on therapy outcome (Hier et al., 1983; Jesshope et al., 1991). Furthermore, anosognosia is an essential problem for therapeutic success (Jehkonen et al., 2006). Many patients with large right-hemispheric lesions show a combination of spatial neglect, visuospatial deficits and anosognosia (e.g., Karnath & Rorden, in press; Kerkhoff, 1998). Research on possible therapeutic approaches has primarily dealt with spatial biases in neglect (for review, see Kerkhoff & Schenk, in revision), showing positive effects of neck muscle vibration (Schindler et al., 2002), prism adaptation (Rossetti et al., 1998; Saevarsson et al., 2009), vestibular (Karnath, 1994), optokinetic (Keller et al., 2009; Mattingley et al., 1994), and theta burst stimulation (Nyfeller et al., 2009).

Yet, there is also evidence suggesting some efficacy of visuospatial and -constructive therapy. Successful approaches with regard to the therapy of visuospatial and -constructive disorders include visuospatial training by feedback (Kerkhoff, 1998; Weinberg et al., 1982), visuoconstructive training (Young et al., 1983), and ADL-therapy. For instance, the graded training of spatial-perceptual capacities with verbal feedback (which is assumed to recalibrate spatial perception) was found to reduce visuospatial deficits (Weinberg et al., 1982). However, apart from those for neglect, only few treatments for visuospatial deficits have been evaluated quantitatively.

Perceptual learning and plasticity

In healthy subjects, recent research revealed beneficial effects of perceptual learning on various perceptual and cognitive functions (for reviews, see Fine & Jacobs, 2002; Goldstone, 1998). Perceptual learning refers to an increase in sensory sensitivity and perceptual judgement after repeated practice. In visual perception, performance in several tasks was shown to improve with practice, including orientation discrimination (Schoups et al., 1995; Shiu & Pashler, 1992; Vogels & Orban, 1985). However, the underlying neural mechanisms are not fully understood and research on perceptual learning is inconsistent with regard to restrictions of learning (i.e., the extent of transfer effects).

Vogels and Orban (1985) found improvements in visual orientation discrimination after practice which did not transfer to unpracticed orientations or other retinal locations. A lack of transfer supports the suggestion that perceptual learning occurs at early stages of processing and is, therefore, restricted to sensory areas addressed by an individual stimulus or task (Fahle, 2005; Fahle & Skrandies, 1994; Sagi & Tanne, 1994). However, other studies found that improvements achieved through perceptual learning can generalize (Fahle, 2005; Polat, 2009), depending on the trained function and task complexity (e.g., Leonards et al., 2002). For instance, Polat (2009) investigated improvements of visual functions through perceptual learning in persons with impaired visual function (amblyopia) and showed that improvements were not restricted to the trained task (contrast sensitivity), but transferred to other visual functions (e.g., visual acuity), indicating plasticity at higher levels of visual processing. These results encourage the use of perceptual learning in neurorehabilitation. Thereby, the generalization of a trained task to other functions is not only important for a better understanding of the neural mechanisms underlying learning, but serves as an indicator of the practical value of training procedures. It is, therefore, necessary to identify factors critical for the transfer or generalization of basic visual functions to further visual functions and tasks.

Rationale of the present study

The present study investigated effects of repetitive feedback-based visual line orientation training on orientation discrimination itself and on further visuospatial and -constructive performance in patients with profound visuospatial disorders. Although some clinical studies showed improvements of visuospatial performance with systematic training of perception in these patients (Weinberg et al., 1982; Young et al., 1983), there are still only few effective therapeutic interventions for severe visuospatial disorders (apart from neglect). In healthy subjects, recent research revealed beneficial effects of perceptual learning on various perceptual and cognitive functions (for reviews see Fine & Jacobs, 2002; Goldstone, 1998). Rapid improvements were demonstrated in the perceptual learning of spatial line orientation (Schoups et al., 1995; Shiu & Pashler, 1992; Vogels & Orban, 1985). In stroke patients, comparable studies are rare and perceptual learning of line orientation has not yet been investigated.

Here, we investigated 13 stroke patients showing deficits in line orientation and related visuospatial tasks in a feedback-based, computerized training of visual line orientation. Patients performed a visual orientation discrimination task and further visuospatial and –constructive tasks before and after repetitive judgement of an oblique line orientation (45°) including visual feedback over 11 (mean) treatment sessions. We addressed the question whether (1) there is a beneficial effect of repetitive feedback-based training of the 45° orientation on visual line orientation discrimination. More precisely, we were interested in whether improvements are limited to the 45° orientation or transfer to other oblique orientations. Furthermore, we investigated whether there is (2) transfer of training on the subjective visual vertical and horizontal (SVV, SVH), which are often disturbed in patients with parietal lesions (Pérennou et al., 2008), (3) interocular transfer, and (4) 'far' transfer to other measures of visuospatial and -constructive performance. Finally we analyzed (5) if a potential improvement persists over time and is equivalent in a follow-up test.

2.4.3. Methods

Participants

Thirteen patients with single, vascular lesion and no evidence of brain stem lesions (as revealed by CT/MRI and clinical symptoms) were included in the study, 11 patients with right-hemispheric, two with left-hemispheric lesions. Table 1 summarizes the demographic and clinical data, including etiological and anatomical information from CT/MRI. Ten patients had parietal cortical lesions, three patients had thalamus or basal ganglia lesions. Mean age was 45.6 years (23-60), mean time since lesion was 20.7 weeks (12-28). Twelve patients were righthanded, one lefthanded. All had normal visual acuity. None of the patients had disease of the anterior visual pathways as judged from orthoptic and ophtalmological investigations (fundus examination, slit lamp). Nine patients had leftsided homonymous visual field deficits (7 hemianopia, 2 hemiamblyopia). Aphasia was ruled out in patients with left-hemispheric damage on the basis of the Aachen Aphasia test. All patients showed profound spatial disorders and visual neglect (neglect screenings described below). Informed consent according to the Declaration of Helsinki II was obtained from all participants.

Visual perimetry and neglect tests

Binocular visual fields were mapped with kinetic perimetry in all patients (see Kuhn et al., 2010). A screening for visual neglect (on white paper 29.7x19.7 cm) included copy drawing (star, daisy, clock, house, face), horizontal line bisection of a 20 cm x 1 mm black line, and number cancellation (10 targets in each hemispace among 100 numbers on the sheet). In addition, a reading test with 180 words sensitive to neglect was administered (Kerkhoff et al., 1992). Omissions or distortions of the left half of copied figures were interpreted as indicator of neglect. Further cut-offs were deviations of more than 5 mm from the true midpoint in line bisection, more than 1 omission in each half of the sheet in number cancellation, and more than 2 omissions or substitutions of letters / words or prolonged reading times (> 120 sec).

Table 1: Demographic and clinical data of the patients.

Nr	Age	Sex	Educ. years	Etiology	Lesion locus	TSL weeks	Hemi-plegia	Visual Field / Field Sparing (°)	Visual Neglect	Line orientation judgement	Visuo-constr. deficit	Practice sessions (trials)
1	40	F	10	ICB right, MCI right	Parietal	12	L	Left hemianopia, 1°	+++, L	0 / 22	0 / 3	14 (221)
2	32	F	8	MCI right	Parietal	12	-	Normal	++, L	22 / 57	8 / 8	11 (224)
3	42	F	11	ICB left, MCI left	Parietal	24	-	Normal	+, R	0 / 57	4 / 5	11 (245)
4	41	M	13	MCI right	Parietal	24	L	Left hemianopia, 2°	+++, L	0 / 11	3 / 3	19 (504)
5	60	M	8	MCI right	Parietal	24	L	Normal	+++, L	0 / 57	0 / 5	17 (525)
6	45	F	12	ICB right	Fronto-parietal	24	L	Left hemiamblyopia, 20°	++, L	0 / 57	3 / 7	13 (250)
7	57	M	11	PCI (Calcarina) right, ICB right	Occipital, thalamic	24	L	Left hemianopia, 2°	+, L	40 / 74	4 / 6	10 (188)
8	54	M	14	ICB right	Parietal	12	-	Left hemianopia, 1°	++, L	0 / 22	5 / 6	10 (276)
9	59	M	17	ICB right (Putamen, Claustrum)	Basal ganglia	24	L	Left hemianopia, 2°	+++, L	11 / 40	1 / 5	11 (247)
10	57	M	10	MCI right	Temporo-occipito-parietal	24	-	Left hemiamblyopia, 24°	+, L	0 / 40	6 / 7	6 (107)
11	52	M	9	MCI right	Fronto-parietal	17	-	Left hemianopia, 1°	++, L	0 / 74	5 / 8	7 (143)
12	23	F	12	ICB right Thalamus	Thalamic	28	L	Left hemianopia, 7°	++, L	11 / 57	1 / 2	10 (135)
13	31	F	8	MCI left	Inferior parietal	20	-	Normal	+, R	0 / 40	1 / 3	8 (170)

Abbreviations: F: female; M: male; Educ.: education (years of schooling); MCI/PCI: middle/posterior cerebral artery infarction; ICB: intracerebral bleeding; TSL: time since lesion; visual neglect: + slight, ++ moderate, +++ severe; L/R: left, right; line orientation judgement: percentile rank in the JLOT before and after training; Visuo-constructive deficit: number of correct items in the Mack-Levine test before and after training;

Visual line orientation discrimination

Visuospatial measurements were taken in darkness with the chassis of the PC-monitor covered by an oval-shaped mask to eliminate visual reference cues. Patients were tested at 0.5 m viewing distance with spectacle corrections where necessary. Head position was stabilized by a head-and-chin rest. Visual orientation discrimination was measured with the computerized 'visual-spatial perception' program (VS, Kerkhoff & Marquardt, 1995). Patients viewed two oblique lines (10 cm x 1.4 mm), oriented differently on the screen. The experimenter rotated one line via mouse clicks, until the patients indicated that both lines had the same orientation. Based on the methods of limits (Engen, 1971), the psychophysical parameters 'constant error' (difference between target and reference line at the point of subjective equality) and 'interval of uncertainty' (range in which lines are perceived as being parallel) were calculated by the program.

Visual orientation discrimination was measured for six angles: 30°, 45°, 60° (tilted clockwise) and 120°, 135°, 150° (tilted counterclockwise). Furthermore, the SVV and SVH were measured via VS. The step-width was 0.5° in all measurements. There were ten trials for each orientation. Orientation conditions were blocked and the sequence of blocks was counterbalanced to control for practice effects. In all conditions, starting position was 20° away from the orientation of the reference line. The direction of initial tilt was counterbalanced to control for effects of rotation direction. Prior to the measurements, patients were familiarized with the experimental setup and performed five practice trials.

Training procedure

Patients performed the described procedure in two baseline sessions before training and one post-training session. The second baseline was collected 6 weeks after the first baseline to control for effects of spontaneous remission. After the second baseline, patients accomplished

4 weeks of training, followed by the post-training session. Additionally, patients performed a follow-up session (only for the 45° and 135° orientation) 8 weeks after the post-training session. In the 4 weeks training, patients practiced the discrimination of the 45° orientation in VS and received perceptual feedback to train the 'correct' orientation (see figure 1). Visual feedback was given via a range of tolerance, which became progressively narrow in the course of training (initial size 20°, stepwidth 1°; final size 8°, stepwidth 0.5°). This range of tolerance was indicated by a rectangular frame around the target line, which was green in case of orientation adjustments within the range and turned red when the target line was rotated out of the range of tolerance. Patients performed an individual number of training sessions and trials, 11.3 sessions (249 trials) on average, ranging from 6-19 sessions (107-525 trials).

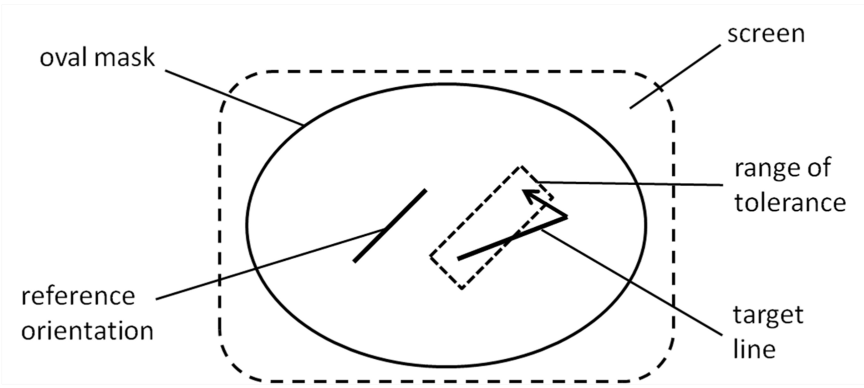

***Figure 1**:* Experimental setup in the visual line orientation discrimination training.

Visuospatial and visuoconstructive tests

To investigate a potential transfer of improvements to related spatial tasks, several measures of visuospatial and -constructive capacities and ADL functions were obtained from the patients. The *Benton Judgment of Line Orientation Test* (JLOT; Benton et al., 1983) is a visuospatial test, requiring subjects to identify the orientation of two target lines on a multiple-choice display with eleven reference lines (the difference of each two being 18°).

The test has two parallel forms, each containing five practice and 30 test items, which were alternated between sessions. The number of errors and performance time were measured. The *Mack-Levine-Test* (Mack & Levine, 1981) is a visuoconstructive test which consists of eight items, each containing several pieces which have to be arranged in the form of a square. Patients had 5 minutes time for each item. Task difficulty was manipulated via the number of pieces and the angle and length of their edges. The number of correct items and performance time were scored. *Analog clock-reading* was assessed in a clock-reading test with two practice and 20 test items. Each item displayed a target clock-face (4 cm diameter) on a 29.7x19.7 cm sheet of white paper with four differently shaped clockfaces (oval, octagon, square, circle). The hands of the target clock-face showed a specific time corresponding to one of the four multiple-choice clock-faces which had to be indicated by the patients. The position of the correct clock-face was pseudo-randomly alternated to control for position biases. The number of correct items was scored. *Horizontal writing* was measured to assess spatial dysgraphia. Patients were required to write their names and addresses horizontally, beginning from the very left of a 29.7x19.7 cm sheet of white paper. This procedure was repeated five times on different sheets of paper. Three patients were unable to perform this task due to hemiparesis of the dominant hand. Deviations from the objective horizontal in degrees were measured and the range of uncertainty and the median of the deviation were calculated.

Monocular training

Two patients (number 4 and 9) performed a monocular orientation training. Their time since lesion was equivalent to control for effects of spontaneous remission. In the monocular line orientation test, one eye was covered by an eye patch in all training sessions. Patient 4 performed 19 training sessions (504 training trials) with the left eye only, patient 9 performed 11 training sessions (247 training trials) with the right eye only. The baseline sessions, the post-training session and the follow-up session were performed monocularly with the trained and nontrained eye in both patients to test whether there is transfer of training from one eye to the other. In these sessions, patients performed six trials for each orientation (30°, 45°, 60°, 120°, 135°, 150°), three with clockwise, three with counterclockwise rotation.

Statistics

To analyze effects of feedback-based training on line orientation performance, repeated measures ANOVAs with the 3-steps factor 'training' (baseline 1, baseline 2, post-training) were performed for the constant errors and intervals of uncertainty in all orientation conditions (30°, 45°, 60°, 120°, 135°, 150°) as well as for the SVV and SVH. Transfer of effects to related visuospatial functions was assessed in equivalent ANOVAs for performance parameters in the JLOT (Benton et al., 1983), the Mack-Levine test (Mack & Levine, 1981), analog clock reading, and horizontal writing. To assess the persistence of training effects, a repeated-measures ANOVA with the 4-steps factor 'training' (baseline 1, baseline 2, post-training, follow-up) was performed for the constant errors and intervals of uncertainty in the 45° and 135° orientation condition. In case of significant main effects or interactions, contrasts were used to compare performance between the different sessions. To assess the extent of interocular transfer (in patients 4 and 9), Pearson correlation coefficients were determined, comparing orientation discrimination performance in the trained and the nontrained eye across training sessions. Spearman rank correlations were calculated to assess the relation between the individual amount of training and the mean training benefit (difference between baseline and post-training performance for mean constant errors and intervals of uncertainty). The alpha-level was chosen as $p<.05$ for all analyses, corrected for multiple comparisons.

2.4.4. Results

Visual line orientation discrimination

Patients showed substantial and systematic tilts in their orientation judgements in the baseline sessions, whereas tilts were strongly reduced in the post-training session (see figure 2). Repeated measures ANOVAs revealed a significant effect of training on the constant errors (*all* $F>17.63$, *all* $p<.001$) and intervals of uncertainty (*all* $F>36.31$, *all* $p<.001$) in all orientation conditions (30°, 45°, 60°, 120°, 135°, 150°). Brain-damaged patients generally displayed significantly larger constant errors and intervals of uncertainty in the baseline sessions compared to the post-training session (*all* $p<.001$). Performance in the two baseline sessions did not differ significantly (*all* $p>.05$). Spearman rank correlations revealed a significant relation between the number of training trials and the reduction of uncertainty intervals ($r=0.64$; $p<0.05$), but no significant correlation between the number of training trials and the reduction of constant errors ($r=0.14$; $p>0.05$).

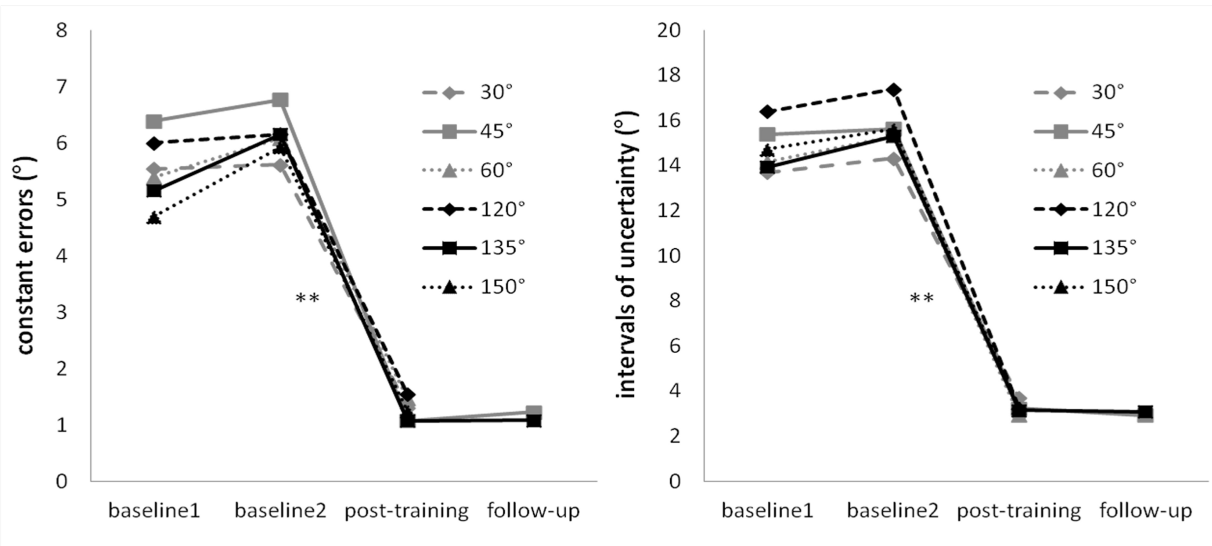

Figure 2: Average visual line orientation discrimination performance (constant errors and intervals of uncertainty) in the two baseline sessions and the post-training session, follow-up performance for the 45° and 135° orientation; positive constant errors indicate counterclockwise tilts of orientation judgements; each line displays one of six orientation conditions (30°, 45°, 60°, 120°, 135°, 150°); ** significant difference between baseline sessions and post-training / follow-up session.

Follow-up

Patients showed comparable tilts of their line orientation judgements in the baseline sessions, but not in the post-training and follow-up sessions (see figure 2). Repeated measures ANOVAs revealed a significant effect of training on the constant errors (45°: $F>31.34$, $p<.01$; 135°: $F>32.67$, $p<.01$) and intervals of uncertainty (45°: $F>41.07$, $p<.01$; 135°: $F>54.81$, $p<.01$). Brain-damaged patients generally displayed significantly larger constant errors and intervals of uncertainty in the 45° and the 135° orientation condition in the two baseline sessions compared to the post-training session, and also compared to the follow-up session (*all* $p<.01$). Constant errors and intervals of uncertainty in the post-training session and the follow-up session did not differ significantly from each other (*all* $p>0.01$).

SVV and SVH

Patients showed comparable tilts of the SVV and SVH in the baseline sessions, but no tilts in the post-training session (see figure 3). Repeated measures ANOVAs revealed a significant effect of training on the constant errors (SVV: $F>10.15$, $p<.01$; SVH: $F>8.38.0$, $p<.01$) and intervals of uncertainty (SVV: $F>11.17$, $p<.01$; SVH: $F>8.44$, $p<.01$). Brain-damaged patients generally displayed significantly larger constant errors and intervals of uncertainty in the baseline sessions compared to the post-training session (*all* $p<.01$) whereas performance in the two baseline sessions did not differ significantly (*all* $p>.05$).

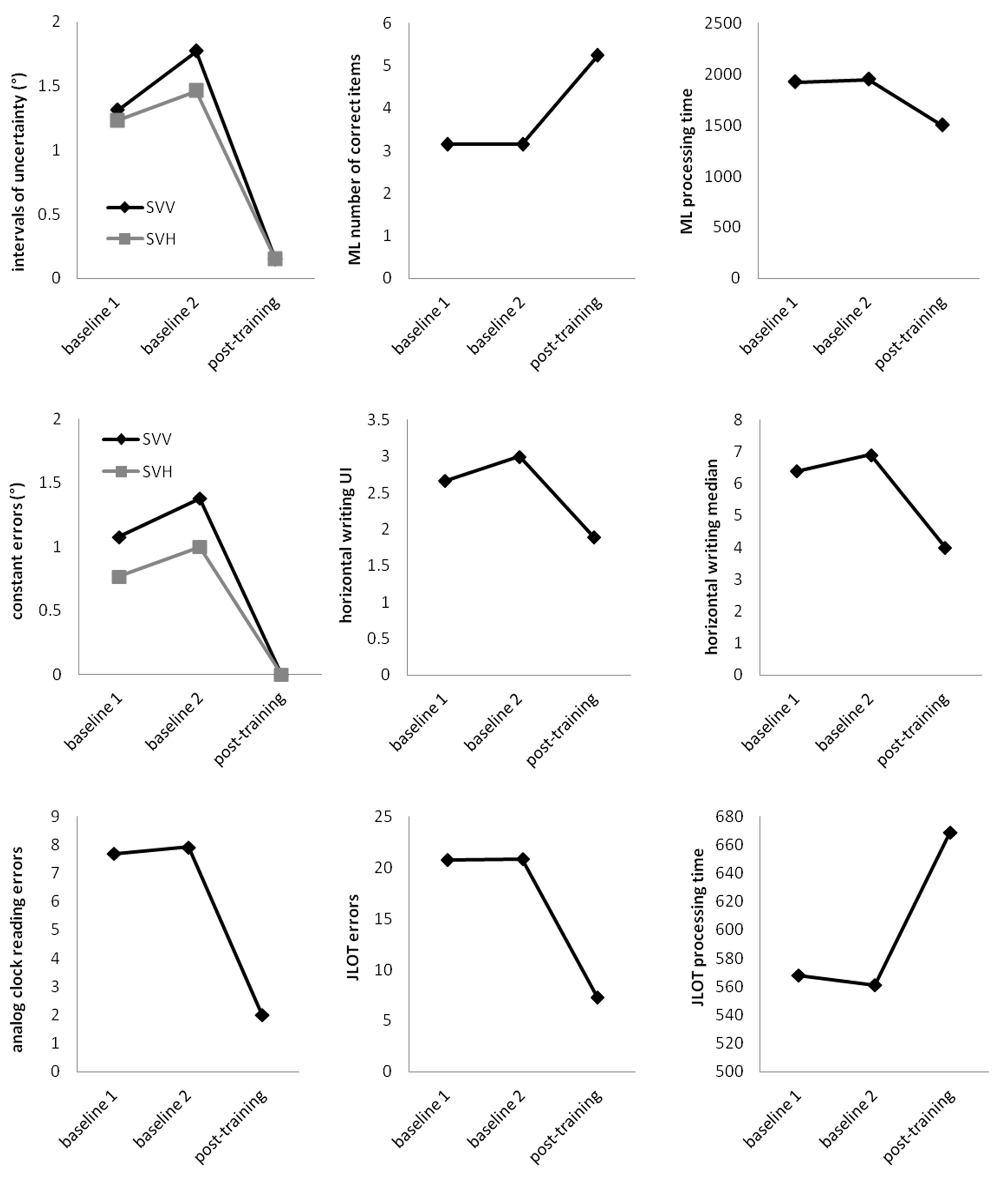

Figure 3: Average performance of patients in the SVV and SVH and measures of visuospatial and –constructive capacities (JLOT, horizontal writing, analog clock reading, Mack-Levine test) for the two baseline sessions and the post-training session; ML, Mack-Levine test; UI, uncertainty intervals in horizontal writing.

Visuospatial and visuoconstructive capacities

Figure 3 displays the average performance of patients in the visuospatial and –constructive tasks for the two baseline sessions and the post-training session.

For the *JLOT* (Benton et al., 1983), repeated measures ANOVAs revealed a significant effect of training on the number of errors (F>87.57, p<.01), percentile ranks (F>67.97, p<.01), and processing time (F>4.28, p<.05). Brain-damaged patients generally displayed significantly less errors, a higher percentile rank, but increased processing time in the post-training session compared to the baseline sessions (*all* p<.01) whereas performance in the two baseline sessions did not differ significantly (*all* p>.05).

In the *Mack-Levine test* (Mack & Levine, 1981), repeated measures ANOVAs revealed a significant effect of training on the number of correct items (F>22.49, p<.01) and the overall processing time (F>13.51, p<.01). Brain-damaged patients generally displayed significantly more correct items and reduced processing time in the post-training session compared to the baseline sessions (*all* p<.01) whereas performance in the two baseline sessions did not differ significantly (*both* p>.05).

For *analog clock reading,* a repeated measures ANOVAs revealed a significant effect of training on the number of errors (F>31.36, p<.01). Brain-damaged patients generally displayed significantly less errors in the post-training session compared to the baseline sessions (both p<.01), whereas performance in the two baseline conditions did not differ significantly (p>.05).

For *horizontal writing,* repeated measures ANOVAs revealed a significant effect of training on the median of the deviation (F>24.12, p<.01), but not the intervals of uncertainty (F>2.25, p>.05). Brain-damaged patients generally displayed smaller deviations in horizontal writing in the post-training session compared to the baseline sessions (*all* p<.01), whereas performance in the two baseline sessions did not differ significantly (*both* p>.05).

Interocular transfer

Figure 4 displays the mean constant errors of patients 4 and 9 across the course of training sessions (11 and 19 sessions, respectively). As can be seen, the curves for the trained and nontrained eyes are nearly identical. Pearson correlations comparing performance between trained and nontrained eyes across training sessions were highly significant for both patients (both r=0.98; p<0.01), indicating nearly perfect interocular transfer.

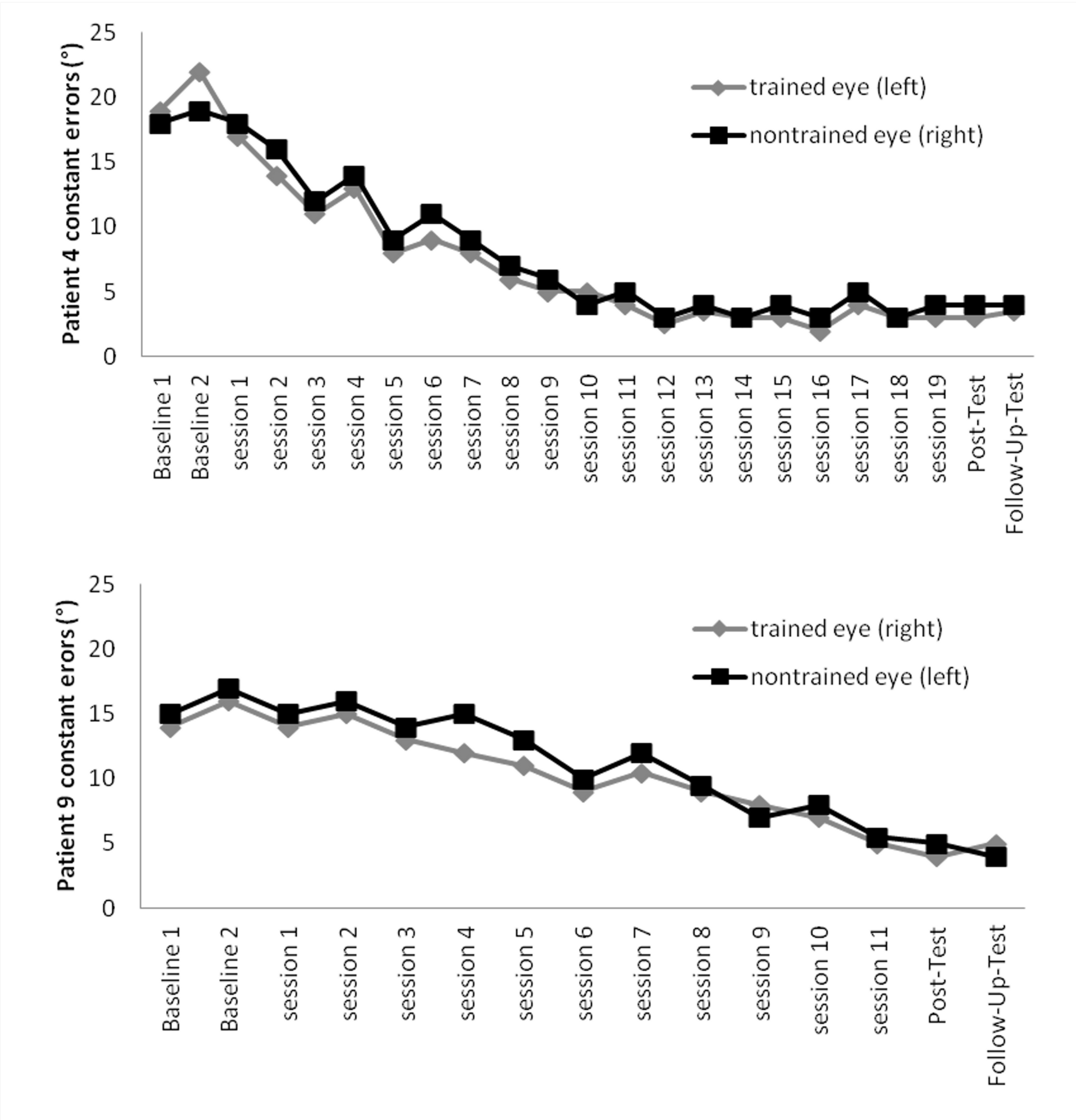

Figure 4: Interocular transfer. Average constant errors of patients 4 and 9 across the course of training sessions for the trained and nontrained eyes. One data point represents the average constant errors across 6 measurements and 6 orientation conditions (i.e., 36 measurements).

2.4.5. Discussion

Patients with large, right-hemispheric lesions show the poorest outcome in neurorehabilitation. In these patients, visuospatial disorders, hemispatial neglect and anosognosia often occur simultaneously. Recent research on therapeutic approaches for these patients has primarily dealt with spatial neglect (for review, see Kerkhoff & Schenk, in revision), but there are still only few effective interventions for severe visuospatial disorders. The present study investigated the effect of repetitive feedback-based training on line orientation discrimination and further parameters of visuospatial and -constructive performance in patients with profound visuospatial disorders. We found clear improvements after only four weeks of therapy (only twelve training sessions on average). There was no improvement across two baseline sessions, indicating that there is no effect of spontaneous remission or repeated testing. Significant improvements occurred in the trained orientation, but also in all untrained orientations as well as the SVV and SVH, indicating a generalized benefit for spatial orientation perception. The significant relation between the number of training trials and the decrease in uncertainty intervals indicates a progressive narrowing of uncertainty intervals with increasing training experience. Training effects were stable in a follow-up session after 8 weeks without training. Furthermore, there was nearly perfect interocular transfer (measured in two patients), that is, equivalent improvements were found for both eyes, even when only one eye was trained. Finally, there was substantial far transfer of improvement to further measures of visuospatial and –constructive performance, including horizontal writing, analog clock reading and visuoconstructive capacities.

Putative mechanisms of improvement

After feedback-based visual line orientation training, RBD patients showed reduced uncertainty intervals and constant errors, indicating a progressive narrowing of uncertainty intervals along with a recalibration of perceptual tilts. Several aspects of the present training data might provide information on the putative stages of visuospatial processing at which feedback-based orientation training affects performance. First, the nearly perfect interocular transfer observed in two patients strongly suggests a postchiasmatic locus for the improvement, beyond V1 where binocular interactions are first seen in primate visual systems (Hubel & Wiesel, 1968). Second, this assumption is supported by the transfer of improvement to nontrained orientations as well as the SVV and SVH, indicating plasticity in higher regions of the dorsal or ventral stream relevant for spatial orientation perception. (Note that, interestingly, healthy subjects were reported not to show transfer to nontrained orientations in perceptual learning of visual orientations; Vogels & Orban; 1985). Finally, the substantial far transfer of improvement to other visuospatial tasks strengthens the assumption of a more central locus for the general improvement at a higher level of visuospatial representation. In line with this view, Polat (2009) investigated improvements of visual functions through perceptual learning in persons with amblyopia and showed that improvements were not restricted to the trained task, but transferred to other visual functions, indicating plasticity at higher levels of visual processing.

Apart from early sensory effects which could be excluded as main agents of improvements, the question arises, which mechanisms might be underlying the observed visuospatial learning effects. In healthy subjects, the (right) parietal cortex seems most critical for orientation processing (Ng et al., 2000; Sack et al., 2001; Taira et al., 1998). Nevertheless, several brain regions contribute to visual orientation discrimination, including V1, the lateral occipital cortex, superior temporal cortex, (right) parietal lobe, and subcortical structures (Faillenot et al., 2001; Shikata, 2003; Vandenberghe et al., 1996). This distributed processing of orientation could be one potential explanation for training benefits despite parietal cortical lesions. Possibly, repetitive feedback-based training enhances the potential of adjacent brain areas of the dorsal and ventral visual system relevant for orientation processing to take over functions of damaged parietal areas. Additionally, training might have stimulating effects on the damaged tissue and enhance neural repair via the sprouting of fibers from surviving neurons with formation of new synapses. Recent research showed that mechanisms of plasticity after brain injury include sprouting of fibers, formation of new synapses, redundancy of brain circuitry with parallel pathways performing similar functions or unmasking of previously existing but functionally inactive pathways (for reviews, see Duffau et al., 2006; Lee & van Donkelaar, 1995; Stein & Hoffmann, 2003). Human brain imaging studies support the concept of functional reorganization after stroke (e.g., Pizzamiglio et al., 1999; Weiller, 1998). Research on functional reorganization after injury furthermore suggests that plasticity does not primarily exist in sensory areas, but is probably even higher in association areas (Kaas, 1991; Kaas et al., 1997). The present finding of generalized improvements after repetitive feedback-based training indicates that the damaged visual system is plastic at higher, or possibly various, levels of visuospatial processing and shows considerable potential to reestablish visuospatial functions as a result of perceptual training.

Role of feedback

Perceptual learning research yielded mixed results regarding the importance of trialwise feedback. To assess the relevance of feedback for training-related improvements (in direction discrimination), Ball and Sekuler (1987) compared data from observers trained with or without trialwise feedback and found that feedback enhanced training effects for oblique, but not cardinal directions. They concluded that feedback might be important for observers training on oblique directions, to sharpen their representation of stimuli they have to discriminate, and less important for observers training on cardinal directions because they already have a clearer, and stable representation of the stimuli. These results indicate that feedback enhances training benefits especially when the representation of stimuli is unclear or unstable, as it is the case in RBD patients with regard to orientation representation. In such patients, trialwise feedback during training might be an important factor of training success. Especially when visuospatial deficits are accompanied by anosognosia, information about the quality and magnitude of the visuospatial deficit is of great importance in rehabilitation. Therefore, feedback should be considered as one essential factor of training success in future rehabilitation studies.

Clinical relevance

The present training effects showed that persistent and generalized improvements in orientation discrimination can be achieved with a rather moderate training effort. The generalization of training effects and the persistence of improvements are indicators of the practical value of the training procedure. Repetitive feedback-based training appears to be an effective, rapid and simple therapy approach for the rehabilitation of visuospatial functions. Importantly, training effects were shown to transfer to other visuospatial and -constructive capacities essential for ADL functions, including horizontal writing, analog clock reading and visuoconstructive capacities. These results encourage the use of perceptual-learning-related approaches in visuospatial rehabilitation. Thereby, it is important to further clarify the underlying changes in central nervous system and use the resulting knowledge for the rehabilitation of patients suffering from sensory or representational deficits after stroke.

Acknowledgements

This work was supported by a Deutsche Forschungsgemeinschaft (DFG) grant to Georg Kerkhoff (IRTG 1457 “Adaptive minds”).

2.4.6. References

Ball, K., & Sekuler, R. (1987). Direction-specific improvement in motion discrimination. *Vision Research, 27(6),* 953-965.

Benton, A.L., Hamsher, K.D., Varney, N.R., & Spreen, O. (1983). *Judgement of line orientation.* New York: Oxford University Press.

Benton, A.L., Hannay, H.J., & Varney, N.R. (1975). Visual perception of line direction in patients with unilateral brain disease. *Neurology, 25,* 907-910.

De Renzi, E., Faglioni, P., & Scotti, G. (1971). Judgment of spatial orientation in patients with focal brain damage. *Journal of neurology, neurosurgery, and psychiatry, 34*, 489-495.

Duffau, H. (2006). Brain plasticity: from pathophysiological mechanisms to therapeutic applications. *Journal of Clinical Neuroscience, 13(9),* 885-897.

Engen, T. (1971). Psychophysics I: Discrimination and detection. In: Kling, J.W., & Riggs, L. (Eds). Woodworth & Schlossberg's experimental psychology (pp11-86). London: Methuen & Co.

Fahle, M. (2005). Perceptual learning: specificity versus generalization. *Current Opinion in Neurobiology, 15(2),* 154-160.

Fahle, M., & Skrandies, W. (1994). An electrophysiological correlate of learning in motion perception. *German Journal of Ophtalmology, 3(6),* 427-432.

Faillenot, I., Sunaert, S., Van Hecke, P., & Orban, G. A. (2001). Orientation discrimination of objects and gratings compared: An fMRI study. *European Journal of Neuroscience*, *13*, 585–596.

Ferber, S., & Karnath, H.O. (1999). Parietal and occipital lobe contributions to perception of straight ahead orientation. *Journal of neurology, neurosurgery, and psychiatry, 67*, 572-578.

Fine, I., & Jacobs, R.A. (2002). Comparing perceptual learning across tasks: a review. *Journal of Vision, 2(2),* 190-203.

Freedman, M., Leach, L., Kaplan, E., Shulman, K. I., & Delis, D. C. (1994). *Clock drawing: A neuropsychological analysis.* New York: Oxford University Press.

Goldstone, R.L. (1998). Perceptual learning. *Annual Review of Psychology, 49,* 585-612.

Hier, D.B., Mondlock, J., Caplan, L.R. (1983). Recovery of behavioral abnormalities after right hemisphere stroke. *Neurology, 33,* 345-350.

Hubel, D.H., & Wiesel, T.N. (1968). Receptive fields and functional architecture of monkey striate cortex. *Journal of Physiology, 195,* 215-243.

Jehkonen, M., Laihosalo, M., & Kettunen, J. (2006). Anosognosia after stroke: assessment, occurrence, subtypes and impact on functional outcome reviewed. *Acta neurologica Scandinavica, 114(5),* 293-306.

Jesshope, H.J., Clark, M.S., Smith, D.S. (1991). The Rivermead Perceptual Assessment Battery: its application to stroke patients and relationship with function. *Clinical Rehabilitation, 5,* 115-122.

Kaas, J.H. (1991). Plasticity of sensory and motor maps in adult mammals. *Annual Reviews in Neuroscience, 14,* 137-167.

Kaas, J.H., Florence, S.L., & Jain, N. (1997). Reorganization of Sensory Systems of Primates after Injury. *The Neuroscientist, 3(2),* 123.130.

Kaplan, J., & Hier, D.B. (1982). Visuospatial deficits after right hemishpere stroke. *The American Journal of Occupational Therapy, 36(5),* 314-321.

Karnath, H.O. (1994). Subjective body orientation in neglect and the interactive contribution of neck muscle proprioceptive and vestibular stimulation. *Brain, 117,* 1001-1012.

Karnath, H.O., & Rorden, C. (in press). The anatomy of spatial neglect. *Neuropsychologia*.

Keller, I., Lefin-Rank, G., Lösch, J., & Kerkhoff, G. (2009). Combination of pursuit eye movement training with prism adaptation and arm movements in neglect therapy: a pilot study. *Neurorehabilitation and Neural Repair, 23(1)*, 58-66.

Kerkhoff, G. (1998). Rehabilitation of visuospatial cognition and visual exploration in neglect: a cross-over study. *Restorative Neurology & Neuroscience, 12,* 27-40.

Kerkhoff, G., & Marquardt, C. (1995). VS – A new computer program for detailed offline analysis of visual-spatial perception. *Journal of Neuroscience Methods, 63,* 75-84.

Kerkhoff, G., Münßinger, U., Eberle-Strauss, G., & Stögerer, E. (1992). Rehabilitation of hemianopic alexia in patients with postgeniculate visual field disorders. *Neuropsychological Rehabilitation, 2,* 21-42.

Kerkhoff, G., & Schenk, T. (in revision). Rehabilitation of spatial neglect: an update. *Neuropsychologia*.

Kim, Y., Morrow, L., Passafiume, D., & Boller, F. (1984). Visuoperceptual and visuomotor abilities an locus of lesion. *Neuropsychologia, 22(2),* 177-185.

Kuhn, C., Heywood, C.A., & Kerkhoff, G. (2010). Oblique spatial shifts of subjective visual straight ahead orientation in quadrantic visual field defects. *Neuropsychologia, 48(11),* 3205-3210.

Lee, R.G., & van Donkelaar, P. (1995). Mechanisms underlying functional recovery following stroke. *Canadian Journal of Neurological Sciences, 22,* 257-263.

Leonards, U., Rettenbach, R., Nase, G., & Sireteanu, R (2002). Perceptual learning of highly demanding visual search tasks. *Vision Research, 42,* 2193-2204.

Mack, J.L., & Levine, R.N. (1981). The basis of visual constructional disability in patients with unilateral cerebral lesions. *Cortex, 17,* 515-532.

Mattingley, J.B., Bradshaw, J.L., Bradshaw, J.A. (1994). Horizontal visual motion modulates focal attention in left unilateral spatial neglect. *Journal of Neurology, Neurosurgery and Psychiatry, 57,* 1228-1235.

Meerwaldt, J.D., & Van Harskamp, F. (1982). Spatial disorientation in right-hemisphere infarction. *Journal of Neurology, Neurosurgery and Psychiatry, 45,* 586-590.

Ng, V.W., Eslinger, P.J., Williams, S.C., et al. (2000). Hemispheric preference in visuospatial processing: a complementary approach with fMRI and lesion studies. *Human Brain Mapping, 10,* 80-86.

Nyfeller, T., Cazzoli, D., Hess, C.W., & Müri, R.M. (2009). One session of repeated parietal theta burst stimulation trains induces long-lasting improvement of visual neglect. *Stroke, 40,* 2791-2796

Pérennou, D., Mazibrada, G., Chauvineau, V., Greenwood, R., Rothwell, J., Gresty, M.A., & Bronstein, A.M. (2008). Lateropulsion, pushing and verticality perception in hemispheric stroke: a causal relationship? *Brain, 131,* 2401-2413.

Pizzamiglio, L., Perani, D., Cappa, S.F., Vallar, G., Paolucci, S., Grassi, F., Paulesu, E., & Fazio, F. (1999). Recovery of neglect after right hemispheric damage. *Archives of Neurology, 55,* 561–568.

Polat, U. (2009). Making perceptual learning practical to improve visual functions. *Vision Research 49,* 2566-2573.

Rossetti, Y., Rode, G., Pisella, L., Farné, A., Boisson, D., & Perenin, M.T. (1998). Prism adaptation to a rightward optical deviation rehabilitates left hemispatial neglect. *Nature, 98,* 166-169.

Sack, A.T., Hubl, D., Prvulovic, D., et al. (2001). The experimental combination of rTMS and fMRI reveals the functional relevance of parietal cortex for visuospatial functions. *Cognitive Brain Research, 13,* 85-93.

Sagi, D., & Tanne, D. (1994). Perceptual learning: Learning to see. *Current Opinion in*

Neurobiology, 4(2), 195–199.

Saevarsson, S., Kristjánsson, Á., Hildebrandt, H., & Halsband, U. (2009). Prism adaptation improves visual search in hemispatial neglect. *Neuropsychologia, 47(3),* 717-725.

Schindler, I., Kerkhoff, G., Karnath, H.O., Keller, I., & Goldenberg, G. (2002). Neck muscle vibration induces lasting recovery in spatial neglect. *Journal of Neurology, Neurosurgery & Psychiatry, 73,* 412-419.

Schoups, A.A., Vogels, R., & Orban, G.A. (1995). Human perceptual learning in identifying the oblique orientation: retinotopy, orientation specificity and monocularity. *Journal of Physiology, 483(3),* 797-810-

Shiu, L.P., & Pashler, H. (1992). Improvement in line orientation discrimination is retinally local but dependent on cognitive set. *Perception & Psychophysics, 52(5),* 582-588.

Shikata, E., Hamzei, F., Glauche, V., Koch, M., Weiller, C., Binkofski, F., et al. (2003). Functional properties and interactions of the anterior and posterior intraparietal areas in humans. *European Journal of Neuroscience*, *17*, 1105–1110.

Stein, D.G., & Hoffman, S.W. (2003). Concepts of CNS plasticity in the context of brain damage and repair. *Journal of Head Trauma Rehabilitation, 18(4),* 317-341.

Taira, M., Kawashima, R., Inoue, K., Fukada, H. (1998). A PET study of axis orientation discrimination. *Neuroreport, 9,* 283-288.

Tartaglione, A., Cocito, L., Bino, G., Pizio, N., & Favale, E. (1983). Further evidence for asymmetry of point localization in normals and unilateral brain damaged patients. Neuropsychologia, 21, 407-412.

Tranel, D., Vianna, E., Manzel, K., Damasio, H., & Grabowski, T. (2009). Neuroanatomical correlates of the Benton Facial Recognition Test and Judgement of Line Orientation Test. *Journal of Clinical and Experimental Neuropsychology, 31,* 219-233.

Vandenberghe, R., Dupont, P., De Bruyn, B., Bormans, G., Michiels, J., Mortelmans, L., & Orban, G.A. (1996). The influence of stimulus location on the brain activation pattern in detection and orientation discrimination. A PET study of visual attention. *Brain, 119,* 1263-1276.

Vogels, R., & Orban, G.A. (1985). The effect of practice on the oblique effect in line orientation judgements. *Vision Research, 25(11),* 679-687.

Weiller, C. (1998). Imaging recovery from stroke. *Experimental Brain Research, 123(1-2),* 13–17.

Weinberg, J., Piasetsky, E., Diller, L., & Gordon, W. (1982). Treating perceptual organization deficits in nonneglecting RBD stroke patients. *Journal of Clinical and Experimental Neuropsychology, 4,* 59-74.

Young, G.C., Collins, D., & Hren, M. (1983). Effect of pairing scanning training with block design training in the remediation of perceptual problems in left hemiplegics. *Journal of Clinical Neuropsychology, 5,* 201-212.

Chapter 3: General Discussion

3.1. Synopsis of results

The rationale of the present project was to conduct a comprehensive series of experiments in order to obtain a clearer picture of the nature and the underlying mechanisms of the spatial deficits in RBD neglect, to systematically analyze the impact of internal and external mediators of spatial biases, and to identify potentially successful intervention schemes for such deficits. Therefore, we investigated (1) spatial orientation deficits in RBD neglect, (2) whether and how such deficits are modulated by *internal* factors mediating the perception of verticality, including body posture and lateral head orientation and by visual context as an *external* mediator of space perception, and (3) by the systematic feedback-based *training* of visual line orientation discrimination.

We found that RBD neglect patients, but not brain-damaged control patients without neglect or healthy controls, generally exhibit a systematic visual-spatial orientation deficit; that is, they generally display a substantial CCW tilt of their visual and tactile SV and oblique orientation judgements. Furthermore, axis orientation performance was differently modulated by internal (body posture, lateral head orientation) and external (visual context) modulators of subjective space perception in RBD neglect patients compared to control patients and healthy controls: SV judgements of all participants varied as a consequence of the respective manipulation; however, performance of neglect patients was far more strongly biased compared to all control groups. They displayed deteriorated performance in supine compared to upright posture, an enhanced 'A-effect' (i.e., a modulation of orientation judgements in the direction of head tilt) as well as an increased rod-and-frame-effect (i.e., a modulation of orientation judgements as a function of frame tilt).

With regard to the effectiveness of feedback-based training of visual orientations, we found rapid improvements in trained but also in non-trained spatial orientations in all 13 patients, partially up to a normal level, after only 4 weeks of training. There was no improvement across two baseline sessions, indicating that there is no effect of spontaneous remission or repeated testing. Significant improvements occurred in the trained orientation, but also in all untrained orientations as well as the SVV and SVH, indicating a generalized benefit for spatial orientation perception. Training effects were shown to be stable in a follow-up session after 8 weeks without training. Furthermore, there was nearly perfect interocular transfer as well as substantial transfer of improvement to further measures of visuospatial and –constructive performance, including horizontal writing, analog clock reading and visuoconstructive capacities.

3.2. Evidence for a supramodal orientation deficit in neglect

In accordance with our prior hypothesis of a multimodal, or supramodal spatial orientation deficit (Kerkhoff, 1999), RBD neglect patients investigated in the present series of experiments showed systematic and analogous tilts of the subjective *visual* and *tactile* vertical and horizontal. The spatial conformity of deviations in both modalities supports the assumption of a disturbed central representation of gravity after parieto-temporal lesions (Brandt et al., 1994). Recently, Pérennou et al. (2008) showed that the most marked visual and tactile tilts in the frontal plane were associated with right parietal lesions where, thus, an internal model of verticality might be elaborated. The assumption of the parietal cortex as the anatomical substrate of a supramodal spatial referece frame is supported by findings referenced above, indicating the existence of multimodal (e.g. Duhamel et al., 1998; Graziano & Gross, 1995) and 'axis-orientation-selective' (Sakata et al., 1997) neurons in the parietal cortex. Damage to such multimodal and orientation-selective neurons might be responsible for the deficits in the perception and representation of the principal spatial axes that become manifest in identical tilts in different modalities. Moreover, cells in the posterior parietal cortex have been reported to contribute to internal models underlying the representation of space by integrating multimodal afferent and efferent / reafferent information (Andersen et al., 1985). Damage to the (right) parietal cortex might therefore lead to a systematic error in the integration of information (as for example somatosensory and graviceptive input) and, thus, to a biased internal representation of space in neglect patients. This is in line with the view that systematic tilts of the coordinate systems can be caused by damage to various parts of a complex system underlying the representation of space, including lesions of the central vestibular pathways (brain stem, thalamus, or vestibular cortex), as well as sensory pathways and (right) parietal lesions (as suggested e.g. by Brandt et al., 1994). The patients examined in the present studies had lesions of structures that are involved in the multimodal representation of space, including the parietal or temporo-parietal cortex and in some cases the thalamus and basal ganglia.

3.2.1. Impaired spatial orientation constancy in neglect

When combining the present findings of a strong influence of *contextual* visual information on the subjective vertical (Funk et al., 2011) and a significant impact of modulations of *internal* mediators of verticality perception (e.g., lateral head orientation: Funk et al., 2010b; and posture: Funk et al., 2010a; Saj et al, 2005b), the emerging picture is one of a loss of *spatial orientation constancy* in patients with neglect. Our results clearly showed that subjective space perception changes significantly and systematically with changes in head- or body-position and visual context. In hemispatial neglect, graviceptive input from the left and right otholitic system is not processed symmetrically (e.g. Pizzamiglio et al., 1995). As a consequence of this impaired processing of vestibular information neglect patients probably cannot rely on a gravitational reference frame, they have to rely on other sources of information mediating subjective space perception to a greater degree than healthy subjects. Therefore, it is assumed that RBD neglect patients show a much stronger impact of e.g.

somatosensory or visual contextual information on subjective space perception. If information from different sources is congruent, that is, if the different frames of reference are aligned, neglect patients show ‘only’ the bias resulting from asymmetric processing (e.g. Pizzamiglio et al., 1995). However, if information from different sources is incongruent, their subjective space perception varies as a function of e.g. somatosensory or visual contextual information and their spatial bias can be enhanced, reduced, or even reversed.

It is likely that the loss of spatial orientation constancy and the pathologically increased influence of internal and external spatial cues have profound consequences in daily life. It can be conjectured that neglect patients have great difficulties in estimating verticality (or spatial orientation in general) in the presence of additional oblique contours visible in the environment and during moving in space and, thus, changing posture and head orientation. That is, depending on the predominant contextual information and on head orientation or body posture, different orientation biases could result which would in turn continuously change through egomotion. This loss of spatial orientation constancy is multimodal and in our view one of the main reasons for the poor postural and mobility capacities typical for neglect patients (Pérennou et al., 2006; 2008). The inaccurate and instable representation of spatial orientations changing with fluctuations in external and internal spatial cues might not only affect fundamental competencies indispensable for managing daily life (e.g., ambulation performance, dressing, transfer from bed to chair), but also performance in clinical tests as well as therapeutic progress. Conversely, internal and external cues modulating the orientation bias in neglect patients might be good candidates to intentionally manipulate the spatial bias in RBD neglect and could therefore be possibly used as potential components of neglect therapy. At least, variations / fluctuations in spatial performance occurring as a consequence of conscious or unconscious modulations of internal and external spatial cues have to be taken into account in the diagnosis and therapy of patients with visuospatial disorders and neglect.

3.3. Putative mechanisms of plasticity following visuospatial training

In the present rehabilitation study, neglect patients showed both smaller intervals of uncertainty and smaller constant errors after repetitive feedback-based orientation discrimination training, indicating a narrowing of uncertainty intervals along with a recalibration of perceptual tilts (Funk et al., submitted). With regard to the putative stages of visuospatial processing at which orientation discrimination training affects performance, the nearly perfect interocular transfer observed in two patients strongly suggests a postchiasmatic locus for the perceptual improvement, beyond the primary visual cortex (V1). This assumption is supported by the transfer of improvement to nontrained orientations, indicating plasticity in higher regions of the dorsal or ventral stream which are relevant for spatial orientation discrimination. Finally, the substantial transfer of training benefits to other visuospatial and –constructive tasks strengthens the assumption of a more central locus for the general improvement at a higher level of (visuo-) spatial representation.

As referenced above, in healthy subjects, the (right) parietal cortex seems to be most critical for orientation processing (e.g., Ng et al., 2000; Sack et al., 2001; Taira et al., 1998). Nevertheless, several brain regions contribute to visual orientation discrimination, including V1, the lateral occipital cortex, superior temporal cortex, (right) parietal lobe, and also subcortical structures (e.g., Faillenot et al., 2001; Riddoch et al., 2004; Shikata et al., 2003; Vandenberghe et al., 1996). This distributed processing of orientation discrimination could be one potential explanation for the positive effects of systematic practice despite the lesions of the parietal cortex. Possibly, repetitive feedback-based training enhances the potential of adjacent brain areas of the dorsal and ventral visual system which are relevant for the processing of orientation to take over parts of the function of the respective brain area affected by the lesion. Alternatively, or additionally, feedback-based perceptual training might have a stimulating effect on the damaged tissue and thereby enhance partial neural repair via the sprouting of fibers from the surviving neurons with formation of new synapses.

Recent evidence from several research fields, including post-stroke rehabilitation, showed that possible mechanisms of plasticity after brain injury include sprouting of fibers, formation of new synapses, redundancy of brain circuitry with parallel pathways performing similar functions (such that an alternative pathway may take over when another has been damaged) or unmasking of previously existing but functionally inactive pathways (for reviews, see Duffau, 2006; Lee and van Donkelaar, 1995; Stein & Hoffman, 2003). Interestingly, research on the reorganization of sensory systems after injury furthermore suggests that plasticity does not primarily exist in primary sensory areas, but in all cerebral areas and is probably even higher in association areas (e.g., Kaas, 1991, 1997).

The present finding of generalized improvements after repetitive feedback-based orientation discrimination training indicates that the damaged visual system is plastic at higher levels, or possibly various levels, of visuospatial processing and shows considerable potential to reestablish visual functions as a result of feedback-based perceptual training.

3.3.1. Clinical relevance of training and transfer effects

The substantial training benefits found in the present study are of high clinical relevance, showing that persistent improvements in orientation discrimination performance as well as a transfer to related visuospatial functions can be achieved with a rather moderate training effort. Especially the generalization of training effects to other functions and the persistence of improvements are indicators of the practical value of the training procedure. Repetitive feedback-based perceptual training appears to be an effective, rapid and simple therapy approach for the rehabilitation of visuospatial functions (like e.g., line orientation discrimination, subjective vertical) which are severely impaired in RBD patients.

Visuospatial disorders are furthermore often accompanied by substantial deficits in ADL functions (Jesshope et al., 1991; Kaplan & Hier, 1982) and show adverse effects on therapy outcome of the patients. The training effects observed in the present study were shown to transfer to visuospatial and visuoconstructive functions essential for ADL functions, including horizontal writing and analog clock reading. These results encourage the use of perceptual-learning-related training approaches in visuospatial rehabilitation. Recent research has shown that perceptual learning improves performance in nearly all tasks investigated, ranging from simple feature discrimination to detecting complex patterns. With regard to rehabilitation procedures, it is important to further clarify the underlying changes in central nervous system and use the resulting knowledge for the rehabilitation of patients suffering from sensory or representational deficits after stroke. Thereby, feedback should be considered as one essential factor of training success in future rehabilitation studies.

3.4. Conclusion

The significant and systematic effects of *contextual* visual information (Funk et al., 2011) and of *internal* mediators of verticality perception (e.g., lateral head orientation: Funk et al., 2010b; and posture: Funk et al., 2010a) on subjective space perception suggest a loss (or at least an impairment) of *spatial orientation constancy* in patients with hemispatial neglect. Put differently: in neglect patients, the perception of the subjective vertical changes dramatically not only with changes in head- or body-position, but also with modifications of contextual visual information that serve as a reference for the perception of spatial orientation. Modulations of internal and external cues mediating the perception of space do affect orientation performance also in healthy subjects or brain-damaged patients without neglect. However, in neglect patients, this modulation is pathologically exacerbated, putatively because they are not able to use intact gravitational information as a reference for the perception of the upright to accurately integrate and counterbalance other sources of input.

The result of this may be an inaccurate and very instable representation of spatial orientations changing rapidly with manipulations of internal and/or external modulators of subjective verticality perception, which has profound consequences in daily life of neglect patients.

On the other hand, the present study showed that patients with visuospatial deficits benefit significantly from repetitive feedback-based perceptual training of orientation discrimination (Funk et al., submitted). We found rapid improvements in trained, but also nontrained spatial orientations, as well as a graded transfer to related (but untrained) spatial tasks in all patients after only four weeks of training, indicating plasticity of the damaged visual system at higher levels of visuospatial processing. These substantial training and transfer effects along with the moderate training effort show a considerable potential for improvements of visuospatial deficits following repetitive feedback-based perceptual training which might yield a better outcome of spatially impaired stroke patients.

In summary, we showed that neglect patients display a systematic bias of spatial orientation perception along with a loss of spatial orientation constancy (studies 1-3), and that both the bias and the uncertainty in subjective space perception can be reduced by feedback-based perceptual training (study 4).

3.5. Future directions

The present study showed relations between spatial neglect and deficits in subjective verticality and orientation perception. The systematic modulability of such deficits by internal and external mediators of subjective space perception is in line with previous findings showing systematic effects of modulations of such mediators – for instance proprioceptive, vestibular, or visual manipulations - on further neglect symptoms (e.g. visual extinction, biases in visual search, or motor neglect; for review, see Kerkhoff & Schenk, in revision). However, recent research on the components of spatial neglect and their respective neural correlates questioned the assumption of a unitary and cohesive syndrome, but rather suggested a multi-componential disorder consisting of dissociable sub-syndromes with distinct neural correlates (Karnath & Rorden, in press; Verdon et al., 2010). One important goal of future research would be to link dissociable co-varying deficits or sub-components to functional units of, for example, the dorsal stream relevant for the processing of the respective spatial (and also non-spatial) functions. A clearer understanding of the behaviorally and anatomically dissociable right hemisphere syndromes would be important to provide clinical as well as theoretical insights. An interesting question with this regard would be whether neglect patient show individual profiles of dissociable and co-varying deficits, or whether there are some basic deficits which can be found in all (or at least a large majority of) neglect patients. For instance, deficits in subjective verticality and orientation perception were found in all neglect patients in the present study, irrespective of their individual lesion sites. Most of the neglect patients tested in the present study had right parietal lesions, but there were also other lesion sites, including temporo-parietal, fronto-parietal, basal ganglia and thalamic lesions. Deficits in subjective verticality and orientation perception would most probably be assigned to a perceptive/visuospatial component of neglect. Interestingly, such a visuospatial component of neglect accounted for the largest amount of variance in the study of Verdon et al. (2010), suggesting that visuospatial deficits are the most prominent symptom in neglect patients.

With regard to the rehabilitation of spatial neglect, the assumption of a multi-componential disorder emphasizes the importance of transfer or generalization of training effects. It is, therefore, necessary to identify not only factors for training success in general, but especially factors which are critical for the transfer/generalization of basic functions to further and also more complex functions and tasks in future neurorehabilitation studies. Furthermore, the preponderance of visuospatial deficits in neglect indicates that it would be important to focus more on these deficits in the rehabilitation of neglect patients in the future.

3.6. References

Andersen, R.A., Essick, G.K., & Siegel, R.M. (1985). The encoding of spatial location by posterior parietal neurones. *Science, 230,* 456-458.

Brandt, T., Dieterich, M., & Danek, A. (1994). Vestibular Cortex Lesions Affect the Perception of Verticality. *Annals of Neurology, 35*, 403-412.

Duffau, H. (2006). Brain plasticity: from pathophysiological mechanisms to therapeutic applications. *Journal of Clinical Neuroscience, 13(9),* 885-897.

Duhamel, J.R., Colby, C.L., & Goldberg, M.E. (1998). Ventral intra-parietal area of the macaque: congruent visual and somatic response properties. *Journal of Neurophysiology, 79*, 126-136.

Faillenot, I., Sunaert, S., Van Hecke, P., & Orban, G. A. (2001). Orientation discrimination of objects and gratings compared: An fMRI study. *European Journal of Neuroscience*, *13*, 585–596.

Funk, J., Finke, K., Mueller, H.J., Preger, R., & Kerkhoff, G. (2010a). Systematic biases in the tactile perception of the subjective vertical in patients with unilateral neglect, and the influence of upright vs. supine posture. *Neuropsychologia, 48(1),* 298-308.

Funk, J., Finke, K., Mueller, Utz, K.S., & Kerkhoff, G. (2010b). Effects of lateral head inclination on multimodal spatial orientation judgments in neglect: Evidence for impaired spatial orientation constancy. *Neuropsychologia, 48(6),* 1616-1627.

Funk, J., Finke, K., Mueller, H.J., Utz, K.S., & Kerkhoff, G. (2011). Visual context modulates the subjective vertical in neglect: Evidence for an increased Rod-and-Frame-Effect. *Neuroscience, 173,* 124-134.

Funk, J., Finke, K., Reinhart, S., Kardinal, M., Utz, K.S., Rosenthal, A., Kuhn, C., Müller, H.J., & Kerkhoff, G. (submitted). Effects of feedback-based visual line orientation discrimination training in visuospatial disorders after stroke. *Neurorehabilitation and Neural Repair.*

Graziano, M.S.A., & Gross, C.G. (1995). The representation of extrapersonal space: A possible role for bimodal, visual-tactile neurons. In Gazzaniga, M.S. (Ed), *The Cognitive Neurosciences* (pp 1021-1034). Cambridge, MA: The MIT Press.

Jesshope, H.J., Clark, M.S., Smith, D.S. (1991). The Rivermead Perceptual Assessment Battery: its application to stroke patients and relationship with function. *Clinical Rehabilitation, 5,* 115-122.

Kaas, J.H. (1991). Plasticity of sensory and motor maps in adult mammals. *Annual Reviews in Neuroscience, 14,* 137-167.

Kaas, J.H., Florence, S.L., & Jain, N. (1997). Reorganization of Sensory Systems of Primates after Injury. *The Neuroscientist, 3(2),* 123.130.

Kaplan, J., & Hier, D.B. (1982). Visuospatial deficits after right hemishpere stroke. *The American Journal of Occupational Therapy, 36(5),* 314-321.

Karnath, H.O., & Rorden, C. (in press). The anatomy of spatial neglect. *Neuropsychologia*.

Kerkhoff, G. (1999). Multimodal spatial orientation deficits in left-sided visual neglect. *Neuropsychologia, 37*, 1387-1405.

Kerkhoff, G., & Schenk, T. (in revision). Rehabilitation of spatial neglect: an update. *Neuropsychologia*.

Lee, R.G., & van Donkelaar, P. (1995). Mechanisms underlying functional recovery following stroke. *Canadian Journal of Neurological Sciences, 22,* 257-263.

Ng, V.W., Eslinger, P.J., Williams, S.C., Brammer, M.J., Bullmore, E.T., Andrew, C.M., Suckling, J., Morris, R.G., & Benton, A.L. (2000). Hemispheric preference in visuospatial processing: a complementary approach with fMRI and lesion studies. *Human brain mapping, 10(2),* 80-86.

Pérennou, D., Mazibrada, G., Chauvineau, V., Greenwood, R., Rothwell, J., Gresty, M.A., & Bronstein, A.M. (2008). Lateropulsion, pushing and verticality perception in hemispheric stroke: a causal relationship? *Brain, 131,* 2401-2413.

Pizzamiglio, L., Vallar, G., & Doricchi, F. (1995). Gravity and hemineglect. *NeuroReport, 7*, 370 –371.

Riddoch, M.J., Humphreys, G.W., Jacobson, S., Pluck, G., Bateman, A., & Edwards, M. (2004). Impaired orientation discrimination and localisation following parietal damage: on the interplay between dorsal and ventral processes in visual perception. *Cognitive Neuropsychology, 21(6),* 597-623.

Sack, A.T., Hubl, D., Prvulovic, D., Formisano, E., Jandl, M., Zanella, F.E., Maurer, K., Goebel, R., Dierks, T., & Linden, D.E.J. (2001). The experimental combination of rTMS and fMRI reveals the functional relevance of parietal cortex for visuospatial functions. *Cognitive Brain Research, 13,* 85-93.

Saj, A., Honoré, J., Davroux, J., Coello, Y., & Rousseaux, M. (2005). Effect of posture on the perception of verticality in neglect patients. *Stroke, 36*, 2203-2205.

Sakata, H., Taira, M., Kusunoki, M., Murata, A., & Tanaka, Y. (1997). The parietal association cortex in depth perception and visual control of hand action. *Trends in Neuroscience, 20*, 350-357.

Shikata, E., Hamzei, F., Glauche, V., Koch, M., Weiller, C., Binkofski, F., et al. (2003). Functional properties and interactions of the anterior and posterior intraparietal areas in humans. *European Journal of Neuroscience*, *17*, 1105–1110.

Stein, D.G., & Hoffman, S.W. (2003). Concepts of CNS plasticity in the context of brain damage and repair. *Journal of Head Trauma Rehabilitation, 18(4),* 317-341.

Taira, M., Kawashima, R., Inoue, K, & Fukada, H. (1998). A PET study of axis orientation discrimination. *Neuroreport, 9(2),* 283-288.

Vandenberghe, R., Dupont, P., De Bruyn, B., Bormans, G., Michiels, J., Mortelmans, L., & Orban, G.A. (1996). The influence of stimulus location on the brain activation pattern in detection and orientation discrimination. A PET study of visual attention. *Brain, 119,* 1263-1276.

Verdon, V., Schwartz, S., Lovblad, K.O., Hauert, C.A., & Vuilleumier, P. (2010). Neuroanatomy of hemispatial neglect and ist functional components: a study using voxel-based lesion-symptom mapping. *Brain, 133,* 880-894.