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Effects of homonymous visual field defects on visuo-spatial perception and performance

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General Abstract

Homonymous visual field defects are typically associated with three distinct types of visual disorders *beyond* the field cut: (i) a visual exploration or scanning deficit, (ii) reading disturbances ("hemianopic alexia"), and (iii) a contralesional visuospatial bias towards the blind field in localizing the midline position ("hemianopic line bisection error", HLBE). While the exploration and reading disorder are well explored and their causes often analysed, the origin of the HLBE – although already known for more than 100 years – have remained largely unclear and are still a matter of debate. The present Ph.D. thesis addresses several unresolved issues of the HLBE in three subsequent, already published studies.

First, it was investigated, whether and to what extent patients with homonymous quadrantranopia display a contralesional visuospatial error when indicating the visual midline. Interestingly, in earlier studies the HLBE was almost exclusively found in horizontal (left or right) or vertical (altitudinal) hemianopia. All 15 tested patients with quadranopia showed distinct and large shifts towards their blind quadrant when estimating their visual subjective straight ahead in a bowl perimeter. Moreover, patients with dorsal lesions respectively lower quadrantanopia showed the largest errors.

Second, the matter of eccentric fixation as a possible cause of the HLBE was analysed in this study and in the subsequent study with patients showing horizontal hemianopia by using the technique of perimetric blind spot mapping. The results revealed in both studies that static fixation as measured by the position of the blind spot(s) was completely normal in nearly all subjects and was neither (cor)related to shifts of the visual straight ahead nor the HLBE. In addition, it was found that the capacity to scan the blind field with saccadic eye movements ("saccadic search field") was not related to the HLBE, thus ruling out visual scanning deficits as a possible cause of the HLBE.

The last issue that was analysed in this thesis was the question of attention in relation to the HLBE. Deficits in line bisection are a frequent finding in patients with visual neglect. Many studies in this context have shown that manipulations of visuospatial

attention, i.e. via attentional cueing to one side of space, significantly modulate the ipsilesional spatial error in patients with visual neglect.

In a similar logic, we evaluated in the second and third study of this thesis, whether attentional cueing to the left or right side of the horizontal line that had to be bisected modulated the HLBE in hemianopic patients. Surprisingly, cueing had virtually no effect on the HLBE in hemianopic subjects while the very same manipulation clearly modulated bisection in a small group of patients with left visual neglect, thus showing the principal efficacy of the attentional manipulation.

In summary, this thesis reports novel evidence of an oblique contralesional spatial error in homonymous quadrantanopia akin to the HLBE in horizontal hemianopia. Moreover, the present results in chronic patients with hemianopia do neither support the notion of eccentric fixation nor of hypo-/hyperattention to one side of space as possible determinants of the HLBE. Furthermore, gross visual exploration deficits do not seem to contribute to the HLBE either. Finally, possible limitations of the present studies are mentioned and alternative theoretical accounts shortly discussed.

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Index of Publications

This doctoral thesis is based on three studies, published in international peer-reviewed journals. The signatory is also the first author of all three publications. All contributiong co-authors are listed below. All papers are presented in the published form, except for changes in formatting (i.e. figure captions). References for all publications are provided at the end of this work.

Content	***has been published as***
Study I	**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), 3250-3210.
Study II	**Kuhn, C., Bublak, P., Jobst, U., Rosenthal, A., Reinhart, S. & Kerkhoff, G.** (2012). Contralesional spatial bias in chronic hemianopia: The role of (ec)centric fixation, spatial cueing and visual search. *Neuroscience*, 210, 118-127.
Study III	**Kuhn, C., Rosenthal, A., Bublak, P., Grotemeyer, K.H., Reinhart, S. & Kerkhoff, G.** (2012). Does spatial cueing affect line bisection in chronic hemianopia? *Neuropychologia*, 50(7), 1656-1662.

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Abbreviations

ANOVA	analysis of variance
BD	brain damaged
BD control	brain damaged control
BG	basal ganglia
cd/m^2	candela per squaremeter
cf.	confer
CHI	closed head injury
cm	centimetre
cm^2	square centimetre
CVI	cerebrovascular insult
e. g.	exempli gratia, for example
Enceph	encephalitis
F	frontal
HA	hemianopia
HLBE	hemianopic line bisection error
HQ	homonymous quadranopia
fMRI	functional magnetic resonance imaging
ICD-10	International statistical classification of diseases and related health problems - 10^{th} revision
i.e.	that is
kLGN	koniocellular LGN part
L/R	left/right
LE/RE	left eye/ right eye
LGN	lateral geniculate nucleus
M	mean
m	metre
m/f	male/ female
MCA	middle cerebral artery infarction
mLGN	magnocellular LGN part
M1	primary motor cortex

min	minute(s)
N Control	normal contraol subjects
O	occipital
Occ	occipital
P	parietal
par	parietal
PCA	posterior cerebral artery infarction
PET	positron emission tomography
PIVC	parieto-insular vestibular cortex
pLGN	parvocellular LGN part
RFL	retinal fixation locus
T	temporal
temp	temporal
TSL	time since lesion onset in months
Tu	tumour operated
VSSA	visual subjective straight ahead

Chapter I: General Introduction

Impaired visual perception due to acquired brain injuries implies far more than the partly loss of vision. Associated visual disorders, such as reduced abilities of reading and visuo-spatial exploration, have been often described (Zihl & Schütt, 2012). Neurological patients with homonymous Hemianopia or Quadrantanopia frequently exhibit further uncertainties to live up to requirements on spatial coordination of voluntary motor functions, such as avoiding obstacles (doorframes, persons, etc.), climbing stairs, fear of falling or reaching for objects. Neurovisually impaired patients often describe those irritations as subtle postural or "vestibular" disturbances impairing their mobility and spatial orientation. They also report a reduced accuracy in gauging distances or angles between their own body and the actually notified target. Theses problems arises especially when the visual target is in the peripheral visual field, similar to patients with optic ataxia (Perenin & Himmelbach, 2012), but more blandly.

In most cases, explicit neuroanatomic correlates for vestibular disturbances are excluded. Neither lesions of the parietoinsular vestibular cortices, nor brainstem affection or disruption within the oculormotor systems are present. As a consequence of these visuoperceptual and visuomotor deficits patients often develop an anxious avoiding behaviour and withdraw themselves from social-communicative and leisure activities, which in turn increases their loneliness, anxiety and depression. Although these disturbances appear to form a clinically prominent syndrome, impeding processes of neurorehabilitation and pandering comorbid affective and anxiety disorders, there are still comparatively few studies analysing these visuospatial and visuomotor deficits in neurological patients with visual field defects.

Considering the fact that visual perceptual disorders are among the most frequent functional disturbances after acquired brain injuries, with an incidence of 20-40% (Clarke, 2005) and rising up to 40-60% of all stroke patients over age 65 (Rowe et al., 2009), it seems worth striving for a better understanding of the visuospatial deficits associated with visual field deficits and their possible origins.

The present doctoral thesis deals with a well-known, clinically frequent but not well-understood visuospatial deficit associated with homonymous visual field defects: the horizontal line bisection error (HLBE). Several unsettled issues around the HLBE such as the possible role of eccentric fixation, attention and visual exploration deficits will be analysed subsequently in three separate studies. The overall aim of this is a better understanding of the possible determinants of the HLBE, which hopefully will enable novel and better neuropsychological treatments for the affected patients.

Before describing the three studies in greater detail, a very short survey of the visual pathways in the brain is given, followed by a description of homonymous visual field defects, their phenomenology, and the HLBE.

1.1 Visual pathways and acquired homonymous visual field defects

1.1.1 Cortical visual pathways

The *optic nerve* emerges from retinal ganglion cells, the third visual afferents, passing through the optic disc. The first visual afferents are generated by the photoreceptor cone and rod cells within the retina, which project onto the retinal bipolar cells, the second visual afferents. The optic nerve is the second out-of-twelve cranial nerve, exiting on each side the orbit to enter the cranial cavity (Trepel, 2012). The part descending from ganglion cells of the nasal hemiretina intersects in the optic chiasm to the opposite optic tract, whereas the temporal part straies uncrossed, constituent the ipsilateral part of the *optic tract*. Hereby, each optic tract consists of axons from both the ipsilateral temporal hemiretina as well as the contralateral nasal hemiretina, so that axons of each optic tract represent the corresponding contralateral visual hemifield (*Fig.1*).

Abbildung Fig. 1 aus urheberrechtlichen Gründen entfernt!

Figure 1 : Visual pathway from retina to the primary visual cortex with related lesions and visual field defects.
(1) optic nerve (2) optic chiasm (3)optic tract (4) lateral genicuale nucleus, LGN (5) optic radiation (6) primary visual cortex (7) sulcus calcarinus; **From:** Neuroanatomie. Stuktur und Funktion"by Trepel, M., Ch. 9.7, p. 237, Copyright 2012 by Elsevier GmbH, Urban & Fischer.

The optic tract aims in the corresponding *lateral geniculate nucleus* (*LGN*) where nearly 90% of its axons switche over to the fourth visual afferents and turn into the optic radiation, the geniculo-striate-pathway (Trepel, 2012). The remaining 10% wire up to the thalamic superior colliculus, the area pretectalis (pretectum) and tectum of the midbrain as well as to the suprachiasmatic nucleus of the hypothalamus (Duus, 2001).

While the LGN, as the starting point of the optic radiation into the visual cortex, ensures the visual perception by projecting retinal visual inputs onto the visual cortical areas, the superiores colliculi enable reflexes, like the corneal reflex, and intentional eye movements in general. The tectum and pretectum are crucial for pupillary light reflexes. Circadian rhythms and hormonal sways are controlled by the hypothalamic suprachiasmatic nucleus.

The LGN neurons have different functional properties depending of retinal ganglion cells they originate from (Gutnisky & Dragoi, 2008). They respond monocularly, i.e. to stimulations of one eye only, and have concentric receptive fields. The LGN neurons are segregated into three different cell types which laminate sextuply the fibers of the optic tract: Magnocellular (mLGN), parvocellular (pLGN) cells and koniocellular neurons (kLGN).

The mLGN cells are the largest cells and structure the two bottommost layers, the four upper layers consist of thinnish pLGN cells and the slimmest kLGN cells form interlayers between those thicker principal stratums (Ferrera, 1994).

The optic tract blends after the LGN into the *optic radiation* transmitting visual impulses through the basal segment of the internal capsule into the receiving areas of the occipital lobe. The optic radiation runs to the anterior part of the temporal lobe, belting the inferior horn (cornu temporale) and posterior horn (cornu occipital) of the lateral ventricles (Meyer's loop) before ending into the primary visual cortex. This run explains why quadrantanopia are quite common after damages to the Meyer's loop (Chen et al., 2009).

The primary visual cortex (also V1 or Brodmanm Area 17) is defined by the course of the sulcus calcarine, taking up the medial part of the occipital lobe and extending into the occipital pole. The axons of the fourth afferents (LGN) terminate retinotopically in V1, where visual apperception firstly takes place. Each retinal print is exactly mirrored in a certain area of V1.

The central fovea takes up 4/5 of the complete primary visual cortex, including the occipital pole (Trepel, 2012). Because of the stripe-like structure of its substantia grisea the primary visual cortex is also called *area striata*, whereas Brodman areas 18 and 19 form the *extrastriate* visual cortices, where afferent inputs coming from Area 17 are integratively processed. Informations about visually perceiced objects are now fragmented into their physical properties as size, shape, color, location and motion. Anon the extrastriate cortex sends efferents onto superior areas of the visual association cortex, located partly in the parietal as well as in the temporal lobe.

The parietal and temporal lobe provide with their posterior segment and constitute in each case commonly with the anterior part of the extrastriate area this functional group. So there is both, a parietal association cortex and a temporal association cortex. The visual association cortex is functionally organized in two different neuroanatomic streams, the *dorsal* and the *ventral* stream.

The *dorsal stream* is supplied by neurons from parietal parts of Brodmann areas 7, also from the middle and superior temporal segments of Areas 37 and 39. It ensures depth vision, spatial orientation, object location, visual motion and movement direction of all perceived objects, which is crucial for acquisition of spatial informations.

The *ventral stream* receives its afferents from the inferior temporal parts (Brodmann areas 20, 37 and 39). The temporal visual association cortex affords shape and color recognition, as well as it connects all perceived objects with the speech regions (via Gyrus angularis), indispensable for object identification. In general, it can be said that the visual association cortex has parietal and temporal localizations, with separately working “where” and “what” streams, whereat each of them processes type-specifically all object informations, coming up from the primary and the extrastriate visual cortices.

Efferents from all visual cortices stray onto the frontal eye field (Area 8) or onto the adjacence between the anterior extrastriate visual cortex and the posterior parietal lobe. The former pilots rapid spontaneous (saccadic) eye movements, the latter eye tracking movements (Somers, Dragoi & Sur. 2002).

1.1.2 Clinical manifestations of homonymous visual field defects

The human visual field is defined as the range which is binocularly perceptible without head- and eye-motion encompassing the horizontal and vertical dimension. A distinction is made between peripheral and central vision. The central visual field extends up to 30° in all directions from the fovea, whereas peripheral vision field areas encompass over nearly 180° on the pitch axis and 100° on the yaw axis (Zihl & Kennard, 2003). The visual field extent can be mapped by manual or automatic perimetry orcampimetry, with fixed head-position in a head- and chinrest.

The most frequent aetiologies of homonymous visual field defects are ischaemic and hemorrhaegic cerebral infarctions, traumatic brain injuries, cerebral hypoxiaand finally, with a lower percentage, neoplastic disorders (Schütt & Zihl, 2012).

Abbildung Fig. 2 aus urheberrechtlichen Gründen entfernt!

Figure 2: Rightsided postchiasmatic brain injuries and their variations of uni-and bilateral homonymous vision field.
1 Hemianopia **2** upper quadrantopia **3** lower quadrantopia **4** paracentral scotoma **5** bilateral hemianopia (tunnel vision) **6** bilateral upper quadrantopia ("upper hemianopia") **7** bilateral lower quadrantopia (lower hemianopia) **8** central scotoma

From: *„Störungen der visuellen Wahrnehmung" by Schütt, S. & Zihl, J. In: Nervenarzt 2012 · 83:1053–1064*
DOI 10.1007/s00115-012-3487-8 Copyright 2012 by Springer Verlag

Visual field defects are generally subdivided into their uni- or bilateral ocurrence, form and magnitude. As shown in figure 2, they can assume a dot-like shape such like paracentral scotoma (4), and their sizes usually vary from smaller stains to much more widespread flats.

As registered in Chapter VII of ICD-10, the 10th Revision of the *International Statistical Classification of Diseases and Related Health Problems,* published by the *World Health Organisation* (2012), visual field defects (ICD-10 H53.4) can involve every single quadrant of the visual field respectively one of its moieties. Homonymous visual field defects are unilateral and contralateral by definitioni.e. they impair congruently the contralesional parts of both eyes's vision to one and the same side.Analogously, bilateral brain lesions can lead to bilateral homonymous visual field loss. Unilateral visual field loss arises in approximately 90% of patients with homonymous visual field defects, wherof homonymous hemianopia constitutes 58%, homonymous quadrantanopia 17% and paracentral scotoma 10% in all cases of visual field loss (Schütt & Zihl, 2012).

Hemianopia (1) denotes vision field loss in one hemifield. Quadrantanopia means blindness of the right or left, upper or lower (2, 3) quadrant of the visual field. Resembling to hemianopia, bilateral complete quadrantopia is also referred to as "upper" (6) or "lower hemianopia" or "altitudinal hemianopia" (7).

Normally, the foveal region (which has a diameter of 1°) is spared from blindness. However, after prolonged cerebral hypoxia a so-called central scotoma (8) with intact peripheral visual field regions may occur.

Tunnel vision (5) exemplifies bilateral homonymous hemianopia, an extreme manifestation of visual loss (e.g. after bilateral occlusions or bleedings of both posterior cerebral arteries, with partial or complete preserveration of the fovea. For the sake of completeness, cortical blindness has to be mentioned.. It occurs as a sequel after destruction of both the laterale corpus geniculate (LCG) and the optic tracts in the course of hypoxic brain damage, for instance after cardiac arrest (Hoyt & Walsh, 1958). Those patients lose all neurovisual capacities all over the whole visual field. According to Schütt & Zihl (2012) 25-30% of patients initially showing a cortical blindness show no remission of their blindness.

Spontaneous restitution from homonymous field loss is quite rare and depends vastly on the size and quality structure of the field loss. The more abrupt the transition of visual sensitivity from the into into the blind field the worseis the prognosis. According to Zhang et al. (2006) the chance of remission declines substantially 3 months after lesion onset, and remains quite unlikely after 3 further months.

Nearly 50% of homonymous hemianopia results from lesions of the lobus occipitalis, 29% are caused by visual pathway injuries and in 21% by lesions of the lateral geniculate nucleus (LGN) and the optic tract (Zihl, 2012).

Visual field defects make up 61.8% of the nosological group of cerebral visual disorders in general. According to Schütt & Zihl (2012) the following visual functions are co-morbidly affected after acquiredbrain injuries: visual acuity and contrast sensitivity (13.4%), light/ dark adaptatation (15.9%), color vision (7.5%), visuospatial perception (30%) and visual recognition (1.4%).

1.2 Visuo-spatial deficits associated with homonymous visual field defects: the horizontal line bisection error (HLBE)

Spatial disturbances occur in the aftermath of both cortical and subcortical lesions. According to Kerkhoff (2012), in 50-70% patients with injuries of the right cerebral hemisphere and 30-50% in cases of lefthemispheric damage show deficits in visuospatial perception and orientation. Visuospatial deficits impair many daily activities.. One particular type of visuospatial error is frequently found in patients with homonymous visual field defects: a contralesional spatial bias when bisecting horizontal lines, termed here the horizontal line bisection error (HLBE, Figure 3).

Abbildung Fig. 3 aus urheberrechtlichen Gründen entfernt!

Figure 3: Overview of different types of visuospatial deficits after acquired brain damage. The line bisection error is described under "Halbierung". The green mark within the horizontal bar indicates the contralesional bisection error in a patient with rightsided hemianopia, the red mark that of a patient with leftsided hemianopia. **From**: Kerkhoff & Utz, (2014). In: Karnath, H.O., Ziegler, W., Goldenberg, G. Kognitive Neurologie und Klinische Neuropsychologie. Berlin: Springer.

1.3 Explanations of the horizontal line bisection error

A recent viewpoint article by Kerkhoff & Schenk (2011) addresses some of the unsettled theoretical issues around the HLBE. Three main issues relevant for the present thesis will be shortly addressed here. These include the question of oculomotor adaptation and eccentric fixation, the role of exploration deficits and of spatial attention as potential determinants of the HLBE.

1.3.1 Oculomotor adjustment strategies exemplified by eccentric fixation

Eccentric fixation is a well circumscribed oculomotor adjustment in patients with central scotoma (Guez, Le Gargasson, Rigaudiere & O'Regan. 1993). Affected patients develop a new retinal fixation locus (RFL) towards the intact area of the retina in order to bypass the field of macular lesion. Further findings even postulate the existence of two loci of retinal fixation (Lei & Schuchard, 1997), depending on given lighting conditions. Still, the main disadvantage of the eccentric fixation is the lower resolution in comparison with the foveal region. Apparently, the problem of remittent visual acuity can be solved by using greater stimuli, such like longer text lines. This seems to be a highly functional adjustment to regain, at least partly, the ability of reading.

In contrast to central scotoma, the visual field sparing after unilateral brain lesions usually includes the foveal or even macular field area, therefore the visual acuity of those patients is quite normal.. Obviously, in this case an eccentric shift of the fovea would not be necessary to increase the resolution of the cone cells, but to augment the size of the visual search field.

Compensatory eccentric fixation in heminanopics was already observed in earlier times (Fuchs, 1922). Trauzettel-Klosinski showed that patients with homonymous heminanopa develop homonymous eccentric fixation as well as the ability to switch between eccentric and central fixation, depending on the changing requirement of the ongoing visual tasks (Trauzettel-Klosinksi, 1997). The author observed that eccentrically fixating patients shift their new retinal fixation locus into the intact hemiretina by aiming their foveal "landing

points" outside the text-line when reading. Thereby, the midpoint of the visual field with all its coordinates and the visual axis are shifted toward the intact hemifield.

As a consequence, the blind spot is shift and hemianopia appears subjectively displaced towards the omitted hemifield. The most interesting finding is the fact, that eccentric fixation is a dynamic strategy in sensu of oculomotor adjustments, situationally triggered and reversible, back to central fixation. Hence, eccentric fixation cannot be considered as a static phenomenon. Even if the development of a new retinal fixation locus is proven, it collaborates seemingly with the still active, anatomical fovea.

In light of the author's finding that all eccentrically fixating patients have a time since onset of at least six months supports the assumption that eccentric fixation results from behiavoral adjustment and compensation.

1.3.2 Deficits of visual exploration

A rather unexplored question in the context of the HLBE is to what extent the frequently observed visual exploration deficits in homonymous visual field defects may contribute or even cause the HLBE. Especially a patient with a more or less complete hemianopia will have difficulties simultaneously seeing the whole horizontal line when trying to estimate its length and then place the midpoint of the line. Consequently, the patient will have to make multiple saccades and fixations before being able to estimate the midpoint. During this process, multiple perceptual errors or distortions may happen. If this hypothesis bears some weight, the capacity for visuospatial exploration in the blind field should be in some way related to the presence and size of the HLBE. In contrast, if both disorders are independent, a null-relationship should be found. To the best of our knowledge, this issue has not been examined in patients with homonymous field defects.

1.3.3 A possible role of attention

As shown in Fig. 3 above (Utz & Kerkhoff, 2014) the HLBE has its mirrorpart in patients with unilateral visuospatial neglect: those patients show an ipsilesional bisection error, hence away from the "impaired" hemifield/hemispace.

This is in direct opposition to the HLBE which is typically directed to the contralesional side (there are exceptions when using very short lines). Several studies have documented that manipulations of spatial attention, i.e. via spatial cueing to a specific spatial location (i.e. the contralesional part of the line in patients with neglect) significantly modulate the bisection performance (Humphreys & Riddoch, 1994).

This spatial cueing can be explicit as in the above mentioned study by Humphreys & Riddoch, but it can also take the form of an implicit flickering light adjacent to the end of the line or bar which is positioned on the contralesional, left side in patients with left visuospatial neglect (Butters et al., 1990).

The results of these studies have typically been interpreted as evidence in favour of a role of spatial attention (deficits) in patients with left visual neglect. In analogy, one might ask whether patients with the HLBE but without neglect, may benefit from such spatial cueing manipulations when bisecting lines or bars. If so, this would indicate that hypo- or hyperattention to one side of space plays a role in the development of the HLBE.

1.3.4 Topics of the present doctoral thesis

The present thesis addresses several of the above discussed issues in relation to the HLBE in three separate, experimental studies with patients suffering from postchiasmatic sotomata. These issues are summarized graphically in the following figure and linked to the different hypotheses around the HLBE as mentioned above. Afterwards, the three studies are described explicitely.

1.4 Synoptic overview of the underlying key topics

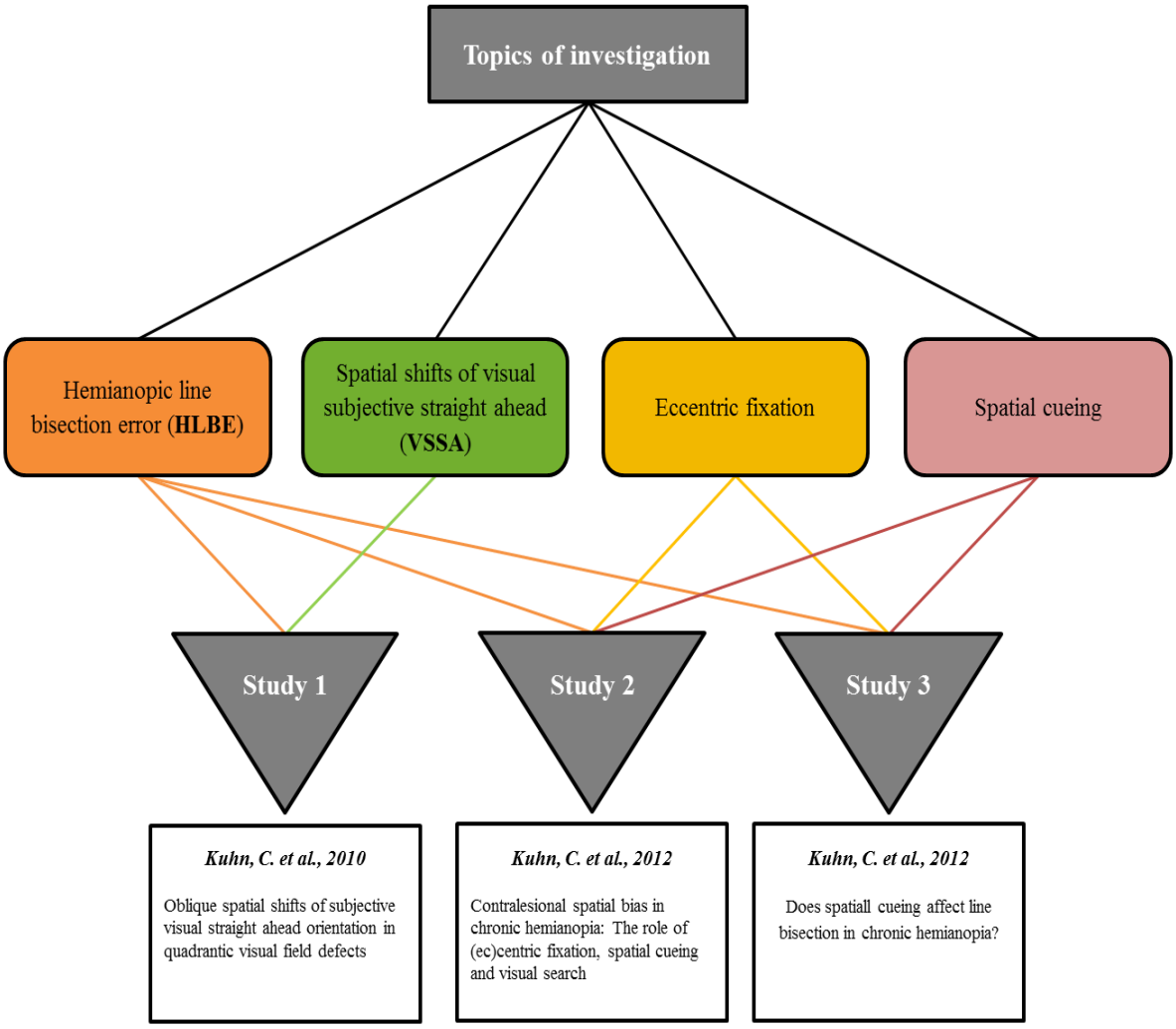

Figure 4: Synoptic view over key topics of the underlying studies this doctoral thesis is based onto.

Chapter II: Studies

2.1 Study I

Oblique spatial shifts of subjective visual straight ahead orientation in quadrantic visual field defects

Kuhn, C., Heywood, C.A & Kerkhoff, G. (2010). *Neuropsychologia*, 48 (11), 3250-3210.

2.1.1 Introduction and rationale

Patients with postchiasmatic visual field defects often show a contralesional bias towards the scotoma in line bisection or when indicating their visual subjective straight ahead (VSSA). Recent evidence suggests a retinotopic misrepresentation of visual space in patients with homonymous quadrantanopia (HQ). We therefore assessed in the present study whether patients with HQ show an *oblique* shift of their VSSA towards their scotoma, in addition to the known bias in horizontal line bisection. Moreover, we examined whether eccentric fixation contributes to this shift. To this purpose, 15 nonneglecting stroke patients with HQ and 15 matched healthy control subjects were assessed in horizontal line bisection and in the horizontal and vertical dimension of their VSSA. Additionally, perimetric blind spot mapping was performed. Eight out of nine patients with left quadranopia showed the typical leftsided, horizontal line bisection error, while only one out of seven patients with rightsided quadranopia showed a rightsided shift. Normal subjects showed a nonsignificant leftward shift in line bisection (pseudoneglect). All 15 patients with HQ showed a large oblique shift of their VSSA towards the blind quadrants, while normal subjects showed no systematic left-rightward shift, but a small downward shift of the VSSA. The position of the blind spot was normal in all testable eyes of patients and control subjects, thus excluding eccentric fixation or cyclorotation of the eyes. In conclusion, our study reveals a hitherto unreported *oblique* spatial shift of subjective visual body orientation towards the blind quadrants in nonneglecting patients with quadranopia.

Homonymous hemianopia is a frequent sequel after stroke (Schofield & Leff, 2009). Hemianopic patients frequently show a peculiar spatial error besides their impairments in reading (Schuett, 2009) and visual scanning (Machner et al., 2009b; Hildebrandt et al., 1999) termed the "hemianopic line bisection error". Axenfeld who coined this term (Axenfeld, 1894) reported that most of his hemianopic patients misplaced the midpoint towards their blind field when bisecting a horizontal line on a sheet of paper. Later investigators have in general confirmed Axenfeld´s early observations (Kerkhoff & Bucher, 2008). Moreover, a recent large-scale patient study has shown that this horizontal spatial error is found in all types of unilateral visual field defects, not only hemianopia (Schuett et al., 2010). Until now, most often *horizontal* deviations in line bisection (Hausmann et al., 2003; Zihl et al., 2009; Doricchi et al., 2005; Barton & Black, 1998) or in the visual subjective straight ahead orientation (Ferber & Karnath, 1999) have been studied although vertical shifts in altitudinal hemianopia have also been reported (Kerkhoff, 1993). While hemianopic patients without neglect show a contralesional, horizontal shift of the subjective visual straight ahead towards the blind field (Ferber & Karnath, 1999) patients with visual neglect - with or without concurrent field defect - often show large ipsilesional shifts of 10-30° (Schindler & Kerkhoff, 2004; Schindler et al., 2002).

An open question is whether quadrantic visual field defects - a "hallmark" of extrastriate visual cortex lesions (Horton & Hoyt, 1991) - also follow this pattern of results. Schuett et al. (Schuett et al., 2010) in their recent study reported that patients with upper or lower homonymous quadrantanopia (HQ) without visual neglect also show the typical *horizontal* line bisection error akin to that seen in patients with left- or right-sided hemianopia (but see Machner et al., 2009a). However, this may not be the only spatial bias that patients with HQ show. Doricchi and co-workers (Doricchi et al., 2003) recently reported a striking, retinotopic dependency of spatial misrepresentation in a patient with left lower and incomplete upper quadrantanopia with mild neglect. This patient misjudged visual distances displayed along different meridians in his blind quadrants. This finding suggests, that patients with HQ may show additional visuospatial misrepresentations beyond those found in the horizontal (left-right) dimension in line bisection.

Moreover, it is known that the hemianopic spatial bias in line bisection is often directed towards the greatest defect in the scotoma: horizontally in left- or right-sided hemianopia

(Barton & Black, 1998; Barton et al., 1998) and a combination of vertical *and* horizontal deviations in patients with altitudinal and lateral visual field defects (Kerkhoff, 1993). If this also applies to HQ, such patients might be expected to show an *oblique* spatial bias towards their blind quadrant(s), in addition to their *horizontal* spatial bias documented previously in horizontal line bisection (Schuett et al., 2010).

Furthermore, an interesting though largely unexplored question is the possible role of eccentric fixation in the emergence of the spatial error in line bisection or in the subjective visual straight ahead. Eccentric fixation has been occasionally reported in hemianopia (Fuchs, 1922; Trauzettel-Klosinski, 1997; Teuber et al., 1960), and discussed as a possible adaptive strategy to compensate for the field loss (Fuchs, 1922, Trauzettel-Klosinski, 1997). As the fixational shift and the line bisection error in hemianopia both are typically directed towards the blind field both might be (cor)related, or eccentric fixation even might cause or exaggerate the spatial shift observed in line bisection. However, bisection judgments, straight ahead judgments and fixation measures were not studied in parallel in these previous studies. In the present study we investigated the judgment of the VSSA in the horizontal and vertical dimension in 15 patients with perimetrically documented HQ, without any sign of visual neglect, and in 15 matched healthy control subjects with perimetrically intact visual fields. Horizontal line bisection was also tested in order to compare the findings in line bisection and the VSSA. In addition, blind spot mapping was performed to explore the role of eccentric fixation.

2.1.2 Methods

2.1.2.1 Subjects

Fifteen patients (11 male, 4 female, mean age: 50.1 years, sd: 10.4) with unilateral HQ after unilateral stroke (n=12) or haemorrhage (n=3) were investigated. None of the 15 patients had visual neglect as determined by 5 conventional tests (Table 1). All patients had a corrected binocular visual acuity of >0.80 for the near (0.4 m) and far (6 m) viewing distance. Fifteen matched healthy control subjects (9 male, 6 female) with normal visual acuity (>0.80 decimal acuity for the near and far) and perimetrically intact visual fields were recruited (mean age: 45.8 years, range: 18-67).

All patients and controls were right-handed according to their verbal report. Neither age (Mann-Whitney-Test, U=92, z=0.395, p>0.05), nor gender (X^2 =3.3, df=1, p>0.05) differed significantly between both samples. All HQ patients were aware of their field defect when asked during the perimetric session, thus excluding anosognosia for their field defect (Celesia et al., 1997). None of the patients showed hemiparesis or hemiplegia, and all showed good verbal comprehension of the instructions.

2.1.2.2 Visual perimetry

Kinetic monocular perimetry was performed in all subjects with a Tuebingen perimeter (Aulhorn & Harms, 1972; Kerkhoff et al., 1994) with a bright white stimulus (size: 106", luminance: 102 cd/m^2), a grey stimulus (106", 1.02 cd/m^2), a coloured target (green 525 nm, same size, 320 cd/m^2), and a form target (white light, same size, rhomboid, 320 cd/m^2). Kinetic perimetry was performed along all meridians in a pseudorandom order. Visual field sparing was determined for the oblique meridian within the blind quadrants (and is indicated in Table 1). Blind spot mapping was performed (monocularly) with a small 35" circular target (white light, 102 cd/m^2) in both eyes where possible (13 patients), or in the ipsilesional eye only (2 patients). The geometric centre of the blind spot of each eye was used for statistics and compared with normative values from the literature (Gradle & Meyer, 1929; Bixenman & von Noorden, 1982). Furthermore, the visual search field, a measure of oculomotor compensation in the visual field, was investigated with the same perimeter in the blind and intact, mirror-symmetric quadrants (details see Kerkhoff et al., 1994). The subject is instructed to search with saccadic eye movements for a circular white target (size: 106´´, luminance: 102 cd/m^2) that is moved by the perimetrist along every meridian from the periphery to the centre with a speed of 2°/sec. The sequence of the meridians tested was random. The patient pressed the response key as soon as the target was detected. This position is scored as the eccentricity of the search field (in °). Here, we selected the median of the search field values of the meridians lying in the *blind* quadrants and compared it with the median of those values obtained in the mirror-symmetric *intact* quadrant. A minimum search field size of 30° in every quadrant is the normal cutoff (Kerkhoff, 1999), and was applied to all HQ patients as a necessary condition for inclusion

in the sample to ensure that they were able to detect the test stimulus in the VSSA test at this eccentricity in all four quadrants (see below).

2.1.2.3 Visual Neglect Tests

Visual neglect was tested with five conventional tests, four of them very similar to those of the Behavioural Inattention Test (Wilson et al., 1987; Halligan et al., 1989): visual search field in the blind and intact quadrants (see above); horizontal line bisection (20 x 0.5 cm long, black horizontal line), cancellation of numerals (30 targets in 200 distracters, 15 in each hemifield), clock drawing from memory, and figure copy (star, flower, cube). Horizontal line bisection was tested conventionally in 3 separate trials with a black horizontal line (20 x 0.5 cm) presented horizontally on a white sheet of paper. All patients used their ipsilesional hand for placing the bisection mark. The median of the 3 trials was used for statistics.

Visual search field is significantly reduced in the neglected hemifield of patients with hemianopia and visual neglect (< 10°, (Kerkhoff et al., 1992) and is therefore a useful screening for visual neglect. All screening tests (including line bisection, but with the exception of the search field test) were shown on a 29.7 x 20 cm white paper board and at a distance of 0.33 m from the patient´s eyes (for more details see Funk et al., 2010).

***Table 1*:** Clinical and demographic data of 15 patients with homonymous quadrantanopia (HQ) without visual neglect.

Patient	Age/ Sex	Etiology	Lesion Localization	Months since Lesion	Quadrantic Field Defect, Field Sparing (°)	Awareness of scotoma	Size of Visual Search Field (blind/intact quadrant,°)	ND	Figure Copy Left/right side	Cancellat. Omissions Left/Right side	Spatial problems (staircase)
1	48,f	R-ICB	T	4	Left upper, 1°	Yes	34/68	no	+/+	0/0	0
2	60,m	R-MCA	T, BG	2	Left upper, 2°	Yes	33/73	no	+/+	0/0	0
3	45,m	R-PCA	O-T	1	Left upper, 2°	Yes	39/72	no	+/+	0/0	0
4	38,m	R-MCA	P	3	Left lower, 6°	Yes	46/68	no	+/+	0/0	1
5	51,f	R-MCA	P	2	Left lower, 32°	Yes	34/68	no	+/+	0/0	1
6	57,f	R-ICB	P	2	Left lower, 22°	Yes	37/70	no	+/+	0/0	1
7	25,m	R-MCA	P-O	13	Left lower, 28°	Yes	38/62	no	+/+	0/0	1
8	50,m	R-PCA	P-O	5	Left lower, 10°	Yes	34/68	no	+/+	0/0	1
9	58,m	R-MCA	P	5	Left lower, 32°	Yes	38/70	no	+/+	0/0	1
10	45,m	L-MCA	T	7	Right upper, 3°	Yes	35/60	no	+/+	0/0	0
11	55,m	L-MCA	T	5	Right upper, 5°	Yes	40/60	no	+/+	0/0	0
12	42,m	L-MCA	T	4	Right upper, 2°	Yes	45/60	no	+/+	0/0	0
13	54,f	L-ICB	O-P	3	Right lower, 4°	Yes	33/70	no	+/+	0/0	1
14	69,m	L-MCA	P-T	4	Right lower, 28°	Yes	30/65	no	+/+	0/0	1
15	55,m	L-PCA/MCA	O-P	3	Right lower, 28°	Yes	33/60	no	+/+	0/0	1
Mean (N=15)	**50.1 (25-69)**	**--**	**--**	**4.2 (1-13)**	**13.6° (1-32)**		**36.6°/66.3°**	**0/15**	**--**	**0/0**	**9/15**

Abbreviations:

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; Visual acuity: decimal letter acuity for near (0.4 m) and far (6 m) viewing condition; Visual Field: Field Sparing is indicated in (°) for the oblique meridian in the blind quadrant. Awareness of visual field defect: patient reports visual field defect during the anamnesis when asked by the experimenter; Spatial problems: indication of subjective problems (Score 1) or no subjective problems (Score 0) in negotiating a staircase up-/downwards when asked in the anamnesis.

Neglect screening tests: Visual Search Field: normal cutoff: 30°; ND=Neglect Dyslexia: 180 word reading test, cutoff: max 2 errors, yes/no: neglect dyslexia present/absent; Figure Copy: - = omissions or distortions; + = normal performance; Cancellation: number of omissions per hemispace, Normal cutoff: max 1 per hemispace

2.1.2.4 Visual Subjective Straight Ahead (VSSA)

The visual subjective straight ahead (VSSA) was tested in total darkness with the same perimeter as used for perimetry but all light sources were extinguished (background illumination and fixation spot). A small red spot (656 nm; 35"; 102cd/m^2) was presented in one of the four quadrants. The subject was instructed to inform the examiner verbally, how to adjust the position of the spot until it was in the visual subjective straight ahead position, both in the horizontal and vertical dimension. Twenty trials were run, 5 each with a starting position from 30° eccentricity on the oblique meridian in the four quadrants (45°-meridian in the right upper quadrant, 135°-meridian in the left upper quadrant, 225°-meridian in the left lower and 315°-meridian in the right lower quadrant). Different starting positions were randomly intermingled in order to exclude effects of starting position on performance of the VSSA. The subject was positioned with his/her head and body positioned straight towards the centre of the perimeter. The head was fixed with a strap to the head- and chinrest of the perimeter so that it remained central during all measurements. The median of the 20 trials was used for statistical analysis and is displayed in Fig. 5.

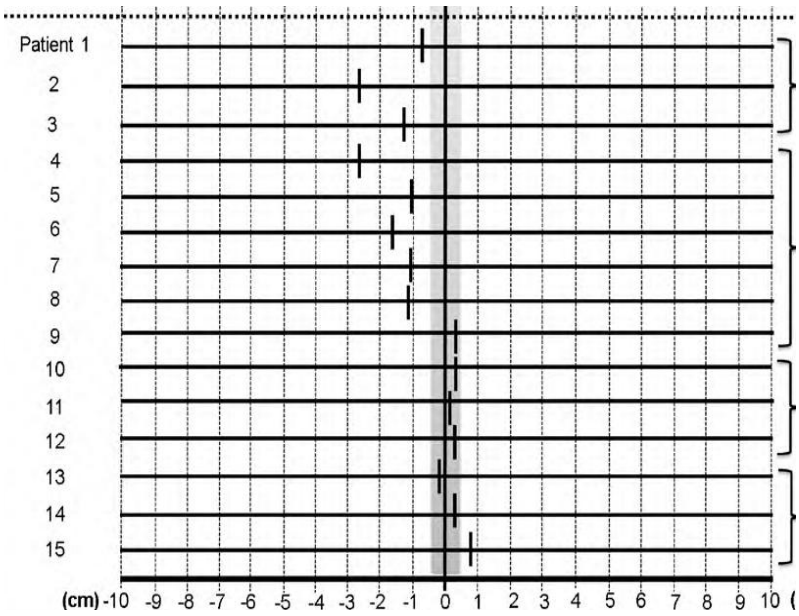

Fig. 5:

Individual results in horizontal line bisection (deviations in cm from the true midline position (0)) in all 15 patients with homonymous quadrantanopia (HQ) and mean deviation in the 15 normal control subjects tested. HQ: homonymous quadranopia. The shaded area indicates the total range of performance in the 15 normal control subjects.

2.1.2.5 Statistics

Nonparametric statistics and one-sample t-tests were computed (SPSS, version 17). The adopted alpha-level was 0.05, two-tailed, corrected for the number of tests by Holm´s procedure (Holm, 1979).

2.1.3 Results

2.1.3.1 Visual field and visual neglect testing

Table 1 summarizes the clinical and demographic patient data. All 15 patients had a homonymous quadrantic visual field defect with some degree of visual field sparing in the blind quadrant, a visual search field of at least 30° in their blind quadrant, good awareness of their visual field defect, and none showed visual neglect according to five conventional screening tests.

2.1.3.2 Horizontal line bisection

Fig. 5 shows the individual results of the 15 patients with HQ, and the mean performance of the 15 normal control subjects. Eight out of 9 patients with leftsided HQ showed a significant, leftsided shift in horizontal line bisection, while only 1/7 patients with rightsided HQ showed the typical shift towards the blind quadrant. Analysis using t-tests confirmed that the group of patients with leftsided HQ deviated significantly from 0 to the left side (mean: - 14.22 mm, df=8, t=-4.349, $p<0.002$). In contrast, the patients with rightsided HQ showed a mean deviation of 2.66 mm to the right side, which was not significantly different from 0 (t=1.896, df=6, $p>.05$) and lay within the normal range (see Fig 5). To test whether visual field sparing on the horizontal meridian within the blind field was related to this significant difference between the two groups of quadrantanopic patients we performed a comparison using independent t-tests. Mean visual field sparing on the horizontal meridian on the blind side was 54.3° (5-77°) in left quadranopia and 32.7° (5-78°) in right quadranopia. The difference is not significantly different (t=1.489, df=13, $p>0.05$).

Moreover, field sparing on the horizontal meridian in the blind field was not significantly correlated in the 15 patients with the deviation in horizontal line bisection (Pearson´s r: -0.3, p>0.05, Spearman´s rho: =-.27, p>0.05). The large field sparing on the horizontal meridian is due to the fact that in many patients the scotoma spared the horizontal meridian (which enabled us to measure the blind spot in so many patients.)

2.1.3.3 Visual Subjective Straight Ahead (VSSA)

Fig. 6 shows the results of the VSSA judgments in both subject groups. All 15 HQ patients showed a significant shift of their VSSA towards their blind quadrant. In contrast, the judgments of all 15 healthy control subjects lay within +/- 2-3° around the true midpoint in the horizontal dimension, but were slightly shifted downwards in the vertical dimension (Fig. 6).

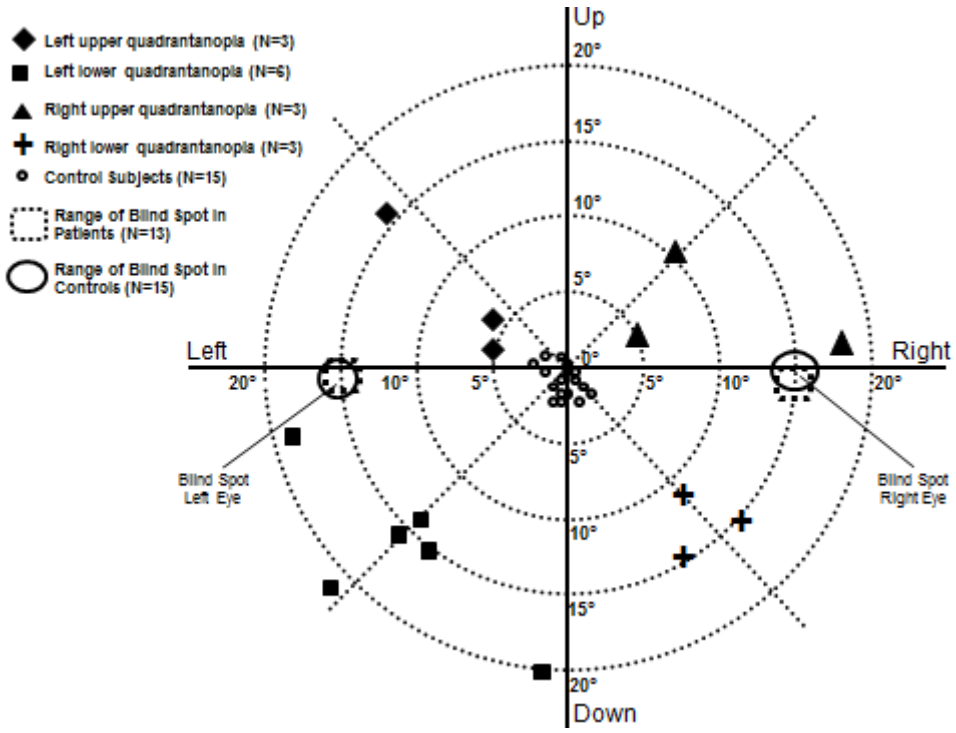

Fig. 6: Summary of individual results in all 15 patients with homonymous quadrantanopia (HQ) and 15 healthy control subjects in the visual subjective straight ahead task (VSSA, see text for details). The median of all 20 trials is displayed graphically for every subject. In addition, the complete range of the centres of the blind spots for the right and left eyes is shown for 13 patients and 15 control subjects. See detailed legend in the left upper part of the figure.

Unsigned errors were used for statistical analysis as the deviations in the different HQ subgroups were in different directions and therefore with different signs. The unsigned *horizontal* error in the VSSA was significantly greater in the HQ patients than in the control subjects (mean HQ: 11.6°, mean controls: 0.8°; Mann-Whitney-Test, U=2.5, p<0.0001). Likewise, the mean unsigned *vertical* error in the VSSA was significantly greater in the HQ patients than in the controls (mean HQ: 8.6°, mean controls: 1.6°; U=28.5, p<0.0001). Moreover, vertical (t=6.31, df=14, p<0.0001) and horizontal (t=8.1, df=14, p<0.0001) deviations of the VSSA were significantly different from the true midpoint (0°-position) in the HQ patients (one-sample t-test). Normal subjects did not differ horizontally in their VSSA from the true midpoint (t=-1.24, df=14, p>0.05), but showed a small, significant downward shift (t=-3.56, df=14, p<0.003). Vertical shifts of the VSSA were larger in patients with *lower* HQ (N=9, mean: 11.1°) vs. *upper* HQ (N=6, mean: 4.9°; U=7.5, p<0.021), and were largest in left lower HQ (mean: 12°, median: 10°, Fig. 5). No difference in *horizontal* shifts of the VSSA between upper and lower HQ emerged (U=26.5, p>0.05). Vertical shifts of the VSSA were significantly correlated (Kendall´s r: 0.395, p<0.05, one-tailed) with subjective problems in negotiating an up- or downwards staircase (Table 1, right column), but horizontal shifts of the VSSA were not (r: 0.013, p>0.05). Inspection of Table 1 shows that only patients with lower HQ acknowledged subjective problems in using stairs, especially downwards, but none of the patients with upper HQ did so. None of the 15 HQ patients was aware of the shift in the VSSA, although all were aware of their quadrantic field defect.

2.1.3.4 Intercorrelations of VSSA and horizontal line bisection

Spearman rank correlations (in the patients) between the *horizontal* line bisection and the *horizontal* error in the VSSA were highly significant (r= 0.68, p<0.01, two-tailed), but the correlation between horizontal line bisection and the vertical error in the VSSA was not (r= -0.08, p>0.05). The horizontal and vertical errors in the VSSA were not significantly correlated in the patients (r=0.08, p>0.05), nor in the healthy control subjects (r=-0.28, p>0.05). Similarly, horizontal line bisection and the horizontal and vertical shift of the VSSA were not significantly correlated with each other (all Spearman correlation coefficients p>0.05, n.s.).

2.1.3.5 Blind spot mapping

Blind spot mapping in both eyes was possible in 13/15 HQ patients (as a result of field sparing around the horizontal meridian) and in all 15 control subjects. The mean horizontal and vertical centre of the blind spot in the left and right eyes of both groups were as follows: HQ: left eye: horizontal: 15.1° lateral to the fovea, vertical: 0.9° below the horizontal meridian. HQ: right eye: 15.0° lateral to the fovea, vertical: 0.7° below the horizontal meridian. Controls: left eye: horizontal: 15.0° lateral to the fovea, vertical: 1.1° below the horizontal meridian; Controls: right eye: horizontal: 15.1° lateral to the fovea, vertical: 0.6° below the horizontal meridian (see Fig. 6). No significant differences were found in any of the paired comparisons with respect to the horizontal and vertical position of the blind spot centre in the right or left eyes of both samples (Mann-Whitney-Tests, smallest p=0.533). Moreover, the position of the blind spot was in the normal range in all 13 patients and all 15 control subjects according to normative data (Gradle & Meyer, 1929; Bixenman & von Noorden, 1982). Hence, eccentric fixation was not present in any case and could not have contributed to the oblique shift of the VSSA in HQ. Moreover, the normal position of the blind spot in both eyes also rules out cyclorotation of the eyes.

2.1.4 Discussion

Patients with HQ – without any sign of visual neglect according to a battery of 5 conventional screening tests comparable to those of the Behavioural Inattention Test (Wilson et al., 1987; Halligan et al., 1989) and good awareness of their scotoma - show a significant (5-20°), *oblique* shift of their VSSA towards their blind quadrant. None of the patients was aware of this subjective shift, but the downward shift was related to subjectively reported problems in visual depth perception during walking up/downstairs. The shift of the VSSA is unlikely to result from insufficient scanning in the blind quadrants since visual search field size within the blind quadrants was within normal limits in *all* HQ patients (≥30°, Table 1). This is in agreement with recent findings in simulated hemianopia where the artificially created field defect impaired eye movements during ocular line bisection, but did not induce the typical hemianopic line bisection error (Schuett et al., 2009) (but see diverging results in another recent study (Mitra et al., 2010).

Together, both observations render a purely oculomotor explanation of the shift of the VSSA in our study unlikely.

2.1.4.1 (Ec)Centric fixation

Similarly, significant eccentric fixation can be ruled out as an explanation for the spatial bias in the VSSA, as the horizontal and vertical positions of the blind spot were normal in all tested subjects and did not differ between both groups. This also rules out a possible *cyclorotation* of the eyes into the blind quadrant as a hypothetical explanation of the oblique shift of the VSSA into this quadrant, as in this case the centre of the blind spots should significantly deviate up or downwards from the normal position typically found slightly (0.5-3°) below the horizontal axis (Gradle & Meyer, 1929; Bixenman & von Noorden, 1982) This however, was not the case in our study (see Fig. 6). As a caveat, it should be mentioned that although blind spot mapping provides a rather precise measure of (ec)centric fixation *during* the perimetric mapping procedure, subtle shifts of fixation might go undetected with this method. Moreover, we can not exclude the possibility that although *static* eye position was normal in all patients with quadrantanopia, *dynamic* eye position (i.e. during ocular scanning or visual straight ahead judgments) may differ in quadranopic patients from healthy control subjects. This question might be addressed in subsequent studies using eye-tracking-devices.

2.1.4.2 Multiple spatial misrepresentations in quadrantic field defects

The horizontal errors observed both in line bisection and in the VSSA were significantly correlated with each other, although not completely coincident, especially not in patients with rightsided HQ, who showed normal line bisection performance despite a contralesional shift of their VSSA. In contrast, horizontal line bisection and the vertical shift of the VSSA showed no correlation. This suggests relative independence of both types of spatial errors and is corroborated by the lack of any correlation between horizontal and vertical errors in the VSSA, both in the patients and control subjects. Hence, the vertical spatial error reported here for the VSSA seems to represent an additional, independent spatial bias apart from the horizontal errors previously reported for line

bisection in HQ (Schuett et al., 2010; Zihl et al., 2009) and the VSSA in hemianopia (Ferber & Karnath, 1999). Apparently, both spatial biases are combined into a new, hithertho unknown *oblique* spatial shift of the VSSA into the blind field in HQ. This shift is directed contralesionally in nonneglecting patients with HQ while it is directed ipsilesionally in patients with visual neglect (Schindler & Kerkhoff, 2004). The present study thus shows that apart from the horizontal bias in line bisection present in many (Schuett et al, 2010) but not *all* patients with quadranopia (cf Machner et al., 2009a) such patients show a hitherto unkown oblique bias in subjective visual body orientation towards their blind quadrant.

In summary, nonneglecting patients with HQ show *multiple* spatial misrepresentations: a) the well-known horizontal line bisection error (Schuett et al., 2010; Zihl et al., 2009) which was present in 8/9 of our patients with left HQ, but only in 1/7 of those with right HQ, b) the oblique shift of the VSSA described here for the first time, and c) the retinotopic-specific spatial misrepresentation of visual distances along different meridians in the visual field (Doricchi et al., 2003).

The significant difference in horizontal line bisection in our patients with left vs. right quadranopia deserves some explanation. As visual field sparing on the horizontal meridian on the blind side did not differ significantly in both groups and was not correlated to the horizontal line bisection error, it is unlikely that the degree of intact field plays a significant role. Rather, it appears that patients with right hemisphere lesions and subsequently left quadranopia more often show a significant shift in line bisection, possible because of the relative dominance of the right cerebral hemisphere, in visuospatial judgments. Indirectly, this suggests that extrastriate cortical areas in the right cerebral hemisphere are more involved in visuospatial coding than those in the left cerebral hemisphere.

The manifold spatial deficits mentioned above probably cause multiple deficits in daily life, including those reported here in walking downstairs in patients with lower HQ. Our findings are compatible with the hypothesis that those extrastriate areas typically lesioned in patients with isolated HQ without neglect contribute to the visual coding of subjective visual body orientation in space, both in the horizontal and the vertical dimension. As patients with lower and upper HQ (respectively dorsal and ventral lesions of

the postgeniculate pathway) showed this spatial error both pathways seem to be involved in this coding. However, the contribution of the more “dorsally” located postchiasmatic pathway seems to be more prominent as patients with lower HQ – subsequent to parietal lesions in all cases (Table 1) - showed the largest vertical errors. The downward shift of the VSSA in normal subjects may reflect an ecological adaptation that biases spatial attention and orientation towards the ground on which we move (Previc, 1990).

2.1.4.3 Conclusions

Nonneglecting patients with quadrantic field defects show a typical, hitherto unknown *oblique* spatial shift of their VSSA into the blind quadrants which is neither due to eccentric fixation or rotation of the eyes, nor impaired scanning in the scotoma, nor neglect. It rather reflects impaired visuospatial coding of subjective visual body orientation due to the postchiasmatic lesion.

2.2. Study II

Contralesional spatial bias in chronic hemianopia: The role of (ec)centric fixation, spatial cueing and visual search

Kuhn, C., Bublak, P., Jobst, U., Rosenthal, A., Reinhart, S. & Kerkhoff, G. (2012). *Neuroscience*, 210, 118-127.

2.2.1 Introduction and rationale

Patients with homonymous hemianopia often show a contralesional shift towards their blind field when bisecting horizontal lines ("hemianopic line bisection error", HLBE). The reasons for this spatial bias are not well understood and debated. Eccentric fixation and adaptive orienting of eye movements towards the blind field have been suggested as hypothetical explanations but were not tested experimentally yet. Moreover, the role of spatial attention and visual search in the blind field are unsettled issues. Here, we tested in 20 stroke patients with chronic homonymous hemianopia (10 left-sided, 10 right-sided) without visual neglect, 10 healthy control subjects and 10 neurological control patients without hemianopia whether the HLBE is related to a) eccentric fixation and b) is influenced by spatial-attentional cueing (left, right) and c) related to the degree of oculomotor compensation in the blind field. Perimetric mapping of the blind spot in the ipsilesional eye was performed in 39/40 subjects. Both hemianopic patient groups showed the typical HLBE towards their blind field, while the two control samples showed only a small but significant leftward shift known as pseudoneglect. The horizontal and vertical position of the blind spot in the ipsilesional eye was within normal limits in 38 out of 40 subjects, and did not differ significantly between the four samples. Moreover, the HLBE was not significantly correlated to the horizontal or vertical position of the centre of the blind spot, thus excluding eccentric fixation as an explanation for this spatial error. Furthermore, spatial cueing by manipulating the starting position of the bisection cue (left, right) did not affect the HLBE, arguing against attentional cueing effects well known from the line bisection error in patients with spatial neglect. Finally, the size of the saccadic search field in the scotoma was not significantly correlated to the HLBE in hemianopia. We conclude, that neither eccentric fixation nor contralesional hyperattention or

ipsilesional hypoattention, nor good or poor oculomotor compensation of the field loss itself are likely causes of the HLBE in chronic homonymous hemianopia. Implications of these findings and alternative explanations are discussed.

2.2.1.1 Rationale of Hemianopic line bisection error (hlbe)

Unilateral lesions of the posterior visual pathways in the human brain often cause contralateral homonymous visual field defects (Miller et al., 2008). Typically, patients with such scotomas show a variety of associated disorders including hemianopic alexia (Kerkhoff et al., 1992; Pflugshaupt et al., 2009; Schuett, 2009; Spitzyna et al., 2007), inefficient visual search in their scotoma (Keller et al., 2010; Lane et al., 2010; Machner et al., 2009) and a peculiar spatial bias towards their blind field when bisecting long horizontal lines or indicating the subjective visual straight ahead (for review see (Kerkhoff and Schenk, 2011). Although completely forgotten for several decades (Kerkhoff and Bucher, 2008) this spatial bias is well known as the hemianopic line bisection error (further termed HLBE) since Axenfeld´s seminal description in 1894 (Axenfeld, 1894). Recent investigations have largely replicated the HLBE (Doricchi et al., 2005; Kerkhoff and Schenk, 2011; Schuett et al., 2010; Zihl et al., 2009) and some showed a relationship to foveal/macular field sparing (Barton and Black, 1998a). Moreover, a recent large-scale patient study has shown that this horizontal spatial error is found in *all* types of unilateral, postchiastmatic visual field defects, not only hemianopia (Schuett et al., 2010b). Apart from *horizontal* deviations in line bisection (Barton and Black, 1998b; Doricchi et al., 2005; Hausmann et al., 2003; Zihl et al., 2009) or in the visual subjective straight ahead orientation (Ferber and Karnath, 1999) vertical shifts in altitudinal hemianopia (Kerkhoff, 1993) or oblique shifts of the subjective visual straight ahead in homonymous quadrantanopia (Kuhn et al., 2010) were also found.

Despite this convergence of results demonstrating the existence of a contralesional spatial-perceptual bias in different types of homonymous visual field defects the precise cause(s) of this error are far from clear and debated (Kerkhoff and Schenk, 2011). Early researchers of the HLBE suggested several theoretical explanations of this error (summarized in Kerkhoff and Bucher, 2008). One prominent account surmised that hemianopic patients show an eccentric fixation towards the scotoma, accompanied by the

development of a new “pseudofovea” located some degrees apart from the anatomical fovea in the blind field (Fuchs, 1922). Although rarely tested experimentally eccentric fixation was occasionally observed in patients with homonymous hemianopia and foveal or macular field sparing (Teuber et al., 1960; Trauzettel-Klosinski, 1997). Some researchers considered this as a kind of compensatory strategy which slightly enlarges the visual field on the blind side and thereby may improve reading (Trauzettel-Klosinski, 1997). Unfortunately, the HLBE was not measured in these studies.

In a similar line of reasoning, the HLBE towards the blind field was viewed as a kind of adaptive, oculomotor strategy which helps the patient to orient his eyes and attention further towards the blind field, which in turn might improve visual orientation and reduce the typical visual problems such as bumping into obstacles or disregarding persons on the blind side (Gassel and Williams, 1963). Moreover, while the eccentric fixation account implies a direct relationship between the HLBE and eccentric fixation the attentional hypothesis that the HLBE is related to attentive or oculomotor orienting to the blind field with the final aim of a better compensation of the field loss predicts a significant relationship between the HLBE and the oculomotor capacity to explore the blind field using scanning eye movements. As we know, that oculomotor compensation clearly improves throughout scanning therapy in hemianopia (Kerkhoff et al., 1994; Lane et al., 2010), and the visual search field in the scotoma is enlarged by about 20° through such rehabilitation procedures (Kerkhoff et al., 1994), one might assume a relationship between this scanning capacity in the scotoma and the contresional HLBE. If scanning capacity is significantly correlated with the HLBE this would suggest a contribution of scanning problems to this error. If not, it appears more likely that the HLBE reflects an independent, visuospatial disturbance with a different origin.

Furthermore, one might argue that if the HLBE reflects attentive orienting towards the blind field, experimental manipulations which direct spatial attention to the blind or seeing side might modulate the HLBE in hemianopic subjects. Interestingly, manipulations of attentional demands during central fixation in a visual field test (perimetry) may induce significant changes in the detection rates for visual stimuli in the periphery – both in young healthy subjects and hemianopic patients with parieto-temporal lesions (Russell et al., 2004). Moreover, Lane and co-workers (Lane et al., 2010) have recently shown that pure attention training induces the same beneficial treatment effects as conventional visual

scanning training in hemianopia. Together, these results indicate a greater role for attention in hemianopia (without neglect) than previously assumed. Moreover, several earlier studies have shown repeatedly that attentional cueing modulates the *ipsilesonal* line bisection error in neglect patients (Riddoch and Humphreys, 1983, Lin et al., 1996).

Finally, the role of brain damage *per se* may be disputed (or the specificity of the HLBE to heminaopia), since the HLBE also occurs in simulated hemianopia *without* brain damage (Mitra et al., 2010). Moreover, *any* brain damage might result in a less accurate judgment of the midline position, regardless of the presence of homonymous hemianopia. To our knowledge, these issues have not been investigated jointly in matched samples of patients with left versus right-sided hemianopia, control patients with acquired brain damage but without a visual field defect, and healthy subjects with intact visual fields. In particular, the eccentric fixation hypothesis has not been evaluated empirically in relation with the HLBE. If eccentric fixation contributes or even causes the HLBE this would indicate the source of the HLBE relatively "early" or on a lower level in the visual processing hierarchy. In contrast, if this is not the case, alternate sources of this visuospatial error, probably located "later" or on higher visual processing stages must be assumed. Finally, it is an open issue whether the HLBE is independent from visuo-motor requirements of the subject. In clinical testing, the hemianopic patient typically bisects *manually* (with a pencil) a horizontal line presented on a sheet of paper (cf (Barton and Black, 1998; Schuett et al., 2011). If the HLBE represents a perceptual bias, it should also be found in a non-motor bisection task. We therefore employed a computerized line bisection task without manual response by the subject to investigate the HLBE in a motor-free task (see below).

The present study therefore investigated three issues: a) Is the HLBE associated with or caused by (ec)centric fixation?; b) Is the HLBE subject to spatial-attentional manipulations ("Cueing") and c) is it related to the capacity of oculomotor search in the scotoma?

2.2.2 Methods

2.2.2.1 Patients and control subjects

20 patients with perimetrically established unilateral, homonymous scotomata following unilateral posterior cerebral lesions (10 left-sided, 10 right-sided; see Table 2, further termed hemianopic=HA patients) and 10 patients with unilateral, cerebrovascular lesions, but with perimetrically intact visual fields were tested (further termed Brain Damaged control patients; Table 2). Stroke was the common aetiology in both the hemianopic sample (n=20, 100%) and the Brain Damaged Control Sample (n=10, 100 %). In addition, 10 normal, dominantly right-handed (handedness-quotient of +100 in all cases) control subjects (8 male, 2 female, mean age 50.5 years; range 22-70) were recruited. None of the healthy control subjects had evidence of ophthalmological, neurological or psychiatric disease. All had perimetrically normal visual fields, and a mean visual acuity of 0.98 (mean, range 0.7-1.2) for the near visual distance (0.4 m) in a standardized letter acuity chart.

2.2.2.2 Handedness questionnaire

Premorbid handedness was determined in all subjects with the German version of the Edinburgh handedness inventory (Salmaso and Longoni, 1985) which measures hand preference. This is expressed as a laterality quotient ranging from -100 (=strongly left-handed) over 0 (=ambidextrous) to +100 (=strongly right-handed; see Table 1).

2.2.2.3 Visual acuity tests

Visual letter acuity was measured separately for each eye with standardized, high-contrast letter charts (Fronhäuser, München, Germany) for the near (0.4 m) viewing distance in all 3 patient samples, and binocularly in the healthy control subjects.

2.2.2.4 Visual perimetry

Binocular visual fields were mapped perimetrically with a Tübingen perimeter (Aulhorn & Harms, 1972) in all patients (for a detailed description see Kuhn et al., 2010), results see Table 2. In short, dynamic visual perimetry was performed with a circular white target (luminance: 102 cd/m^2; size: 1.02 °) in a completely dark room.

Table 2: Patient data*:* L1-L10: Left Homonymous Hemianopia; R1-R10: Right Homonymous Hemianopia

No.	Age (y)/ sex	Aetiology TSL (months)	Lesion Side Localization	Visual acuity near LE/RE (%)	VisualField Sparing (°)	Visual search field (°)	Handedness
L1	69/f	CVI/120	R-occ	50/60	2	35	+100
L2	40/f	CVI/10	R-occ	100/100	14	66	+100
L3	68/m	CVI/12	R-occ	100/100	22	24	+100
L4	63/m	CVI/13	R-occ	60/50	2	25	+100
L5	32/f	CVI/9	R-occ-temp	60/50	1	30	+100
L6	31/f	CVI/2	R-par-temp	125/125	1	10	+100
L7	33/m	CVI/168	R-occ-temp	100/100	2	10	+100
L8	37/m	CVI/6	R-occ	90/90	3	39	+100
L9	32/m	CVI/96	R-temp	90/90	1	30	+100
L10	32/m	CVI/48	R-occ-temp	100/100	2	38	+100
Mean	45.6/-	-/48.4 **Md:** 13	-	87.5/86.5	5.0° **Md**: 2	30.7	+100
R1	44/f	CVI/15	L-occ-temp	70/70	5	22	+33.3
R2	66/m	CVI/4	L-occ-temp	80/80	15	42	+100
R3	42/m	CVI/36	L-occ-temp	80/80	20	55	+60
R4	48/m	CVI/38	L-occ-temp	80/80	3	44	+100
R5	29/m	CVI/8	L-occ	100/90	2	35	+100
R6	58/m	CVI/7	L-occ	90/90	4	28	+100
R7	49/m	CVI/6	L-occ-temp	80/80	1	33	+100
R8	69/m	CVI/3	L-occ	80/70	2	8	+100
R9	62/m	CVI/17	L-occ	100/60	5	10	+100
R10	35/f	CVI/15	L-occ	70/120	2	25	+100
Mean	51.7/-	-/14.9 **Md:**8	-	82.0/82.0	5.9° **Md:** 4	30.2	+89.3

Table 3: Brain damaged control patients (C1-C10)

No.	Age (years) Sex	Etiology TSL (months)	Lesion Side Localization	visual acuity near LE/RE (%)	Handedness
C1	50/m	CVI/6	R-temp-par	90/90	+100
C2	29/f	CVI/7	R-temp	90/90	+100
C3	49/m	CVI/10	diffuse	90/90	+100
C4	55/m	CVI/50	L-BG	-/63	+100
C5	47/m	CVI/15	L-BG	100/100	+100
C6	63/m	CVI/2	L-temp	120/120	+100
C7	59/m	CVI/3	R-front-temp	100/100	+100
C8	48/m	CVI/8	L-temp	100/80	+100
C9	54/m	CVI/7	R-temp	80/80	+100
C10	42/f	CVI/14	L-temp	100/100	+100
Mean	48.6/-	-/12.2 **Md:** 8	-	96.5/95.0	+100

***TSL**: time since lesion onset in months; **L/R:** left/right; o**cc**: occipital, **par**: parietal, t**emp**: temporal, **m/f:** male/female; **LE/RE**: left/right eye; **CVI**: cerebrovascular insult; L/R: left/right; BG: basal ganglia*

2.2.2.5 Oculomotor Search in the Scotoma (Visual Search Field)

We measured the extent of the Visual Search Field - a measure of oculomotor compensation - within the blind and intact visual hemifield. As this test has been described in detail elsewhere (Kerkhoff et al., 1994) only an abridged account is given here. The subject is instructed to search with saccadic eye movements for a circular white target (size: 1.02°, luminance: 102 cd/m^2) that is moved by the perimetrist along every meridian from the periphery to the centre with a speed of 2°/sec. The sequence of the meridians tested was random. The patient presses the response key as soon as he detects the target. This position is scored as the eccentricity of the search field (in °). Here, we selected the horizontal meridian lying in the *blind* hemifield, which was computed as the median of the scores of the six meridians lying in the blind field. A minimum search field size of 30° is the lower normal cutoff (Kerkhoff et al., 1994).

2.2.2.6 Mapping of the Blind Spot

During monocular visual field testing the size and location of the blind spot was determined with a small white circular test target (luminance: 102 cd/m^2; size: 0.06°) with the Tübingen perimeter. In the hemianopic samples the blind spot was registered in the ipsilesional eye (it cannot be determined in the contralesional eye because of the field defect). In the two other samples the blind spot was measured in half of the cases in the left eye, in the other half in the right eye. 20 trials were run in each subject. In each trial the target was initially placed within the presumed centre of the blind spot and then moved sequentially to the upper, lower, left or right side until the subject responded by button-press when perceiving the target. The position was then marked as the border of the blind spot on the diagram. This procedure was repeated 20 times. The centre of the blind spot was determined by inserting a horizontal and vertical axis centrally into the mapping of the blind spot. The centre was expressed as a horizontal deviation (in°) from the fovea and as a vertical deviation (in° from the horizontal axis) for statistical comparisons, and was compared to anatomical data of the normal position of the blind spot in healthy subjects (Bixenman and von Noorden, 1982; Gradle and Meyer, 1929; Hopkins, 1941). Fixation was continuously inspected through the ocular of the perimeter in all trials.

2.2.2.7 Computerized Horizontal Line Bisection Task

Subjects were placed in front of a computer screen (17´´) in a distance of 0.45 m. The head was positioned in a head- and chinrest mounted on a table in front of the screen to prevent head movements during testing. On the screen a white horizontal bar (160 x 10 mm, luminance: 400 cd/m^2) appeared centrally on the black screen. The bar contained a vertical slit (size: 5 x 10 mm) that appeared either on the right end of the bar (test 1, 10 mm away from the end of the bar) or on its left end (test 2, 10 mm away from the end of the bar). The subject was asked to determine verbally when the slit was exactly in the centre of the horizontal bar. To this purpose the examiner moved the slit in steps of 1 mm slowly towards the other side of the bar until the subject indicated that the slit was exactly in the middle of it. Five trials were performed in each test, resulting in a total of 10 trials. Constant errors were computed using the method of limits by special software (Kerkhoff and Marquardt, 1998; Kerkhoff and Marquardt, 2004) between the objective centre of the

bar and the mean position of the slit as determined by the subject. No motor component was involved in this bisection task on the subject´s side, nor was there any time limit.

2.2.2.8 Visual neglect test battery

Five conventional visual neglect tests – comparable to the Behavioural Inattention Test (Wilson et al., 1987) - were performed to rule out visual neglect in our samples: horizontal line bisection of a 20 x 0.2 cm black line on a white sheet of paper; number cancellation (30 targets among 150 distracters, presented on a 29.7 x 21 cm large white paper), drawing of a clock face from memory, copying 3 geometrical figures (a star, a daisy, a face; each on a different sheet of paper) and an indented reading test of 180 words. Neglect was diagnosed when the truncation midline in bisection deviated more than 5 mm to the *ipsilesional* side (Kerkhoff, 1993), when more than 1 target was omitted on one side in number cancellation, when numerals were omitted or misplaced on the left side of the clock face test, or when the subject committed more than 2 reading errors in the indented reading test (Reinhart et al., 2011).

2.2.2.9 Testing conditions

Visual perimetry, the mapping of the blind spot and the experimental line bisection testing took place in a totally darkened room (< 10 Lux room lighting), the only visible stimulus in perimetry and blind spot mapping was the background illumination of the perimeter (3.2 cd/m^2) and the test stimulus. In line bisection testing the only visible stimulus was the horizontal, white bar on the black computer screen. All other (screening) tests took place in a day-lit room (mean lighting: approximately 400 Lux).

2.2.2.10 Statistics

Nonparametric statistics were computed. Paired comparisons were run with Wilcoxon or Mann-Whitney-Tests, which were Bonferroni-corrected for the number of statistical tests. The alpha-level was 0.05 (two-tailed).

2.2.3 Results

2.2.3.1 Comparison of the samples

Statistical comparisons revealed that neither handedness (Kruskal-Wallis-Test X^2=4.341, df=3, p=.227), nor age (X^2=3.097, df=3, p=.377), nor gender (X^2 = 2.88, df=3, p=0.41) were significantly different between the four samples. Visual acuities for the near viewing distance (0.4m) were examined separately for the left and the right eyes. There were no significant differences between the three patient groups in the near viewing distance (left eye: X^2=5.838, df=3, p=.054; right eye: X^2=4.046, df=3, p=.132). Moreover, the three patient groups did not differ significantly regarding time since lesion (median left HA = 12.50 months; median right HA = 11.50 months, median control patients= 7.50 months; X^2=2.271, df=2, p=.321). None of the patients showed any signs of visual neglect in any of the 5 neglect screening tests.

2.2.3.2 *Visual field sparing*

Both hemianopia (HA) samples did not differ significantly from each other in visual field sparing (mean left HA = 5.0°; mean right HA = 5.9°; Mann-Whitney-test, z=-1.242, p=.214). Two out of ten leftsided HA patients showed visual field sparings of 14° and 22°. Among the rightsided HA sample one patient had a field-sparing of 15°, the second of 20°.

2.2.3.3 Spatial Cueing direction

First, we examined whether there was a possible attentional "cueing" effect of the starting point from where the vertical slit was moved by the experimenter towards the middle of the bar. Separate nonparametric Wilcoxon-Tests (for each group) revealed that the starting point of the vertical slit in the 2 bisection tasks had no significant effect on the bisection error in any of the 4 groups (Left HA: z=-.357, p=.721; Right HA: z=-.0058, p=.953; Brain Damaged Controls: z=-.889, p=.374; Normal Controls: z=-.816, p=.415). Therefore, the data of both tasks were collapsed in every subject group and the mean of the two experimental bar bisection tests (one with left and the other with right starting point) was

used for all further statistical calculations. A significant difference between the four subject groups was found for this collapsed bisection error (Kruskal-Wallis-Test, X^2=30.027, df=3, p=.000] which was further examined in the following section.

2.2.3.4 Size of the Horizontal line bisection error

Mann-Whitney- Tests (Bonferroni corrected) revealed that left vs. right hemianopic patients differed significantly from each other in their *signed* bisection errors (z=-3.782, p=.000), but not in their *unsigned* error (z=-.53, p=.631). BD control patients and normal controls did not differ significantly from each other in their bisection performance (z=-.303, p=.796). Left hemianopic patients differed significantly from both control samples (BD control subjects: z=-3.177, p=.001, normal controls: z=-3.291, p=.000), and the same held true for right hemianopic patients (comparison to BD control subjects: z=-3.782, p=.000; comparison to normal controls: z=-3.781, p=.000).

All left hemianopic patients bisected the lines considerably towards the *left* of centre (mean: -6.31 mm) and all right hemianopic patients towards the right of centre (mean: +5.59 mm), hence in both samples towards the blind field (Fig. 7). In contrast, the normal control group (mean= -0.84 mm) as well as the brain damaged patient control group (mean= -0.72 mm) revealed just a slight, but (marginally) significant leftward shift indicative of left pseudoneglect (Jewell and McCourt, 2000). One-sample T-tests (against 0) confirmed a small but significant leftward shift from the objective midline in the bisection test in the healthy control subjects (T(9)=-2.34, p=0.02), and a similar, but nonsignificant trend in the BD control patients (T(9)=-1.51, p=0.08).

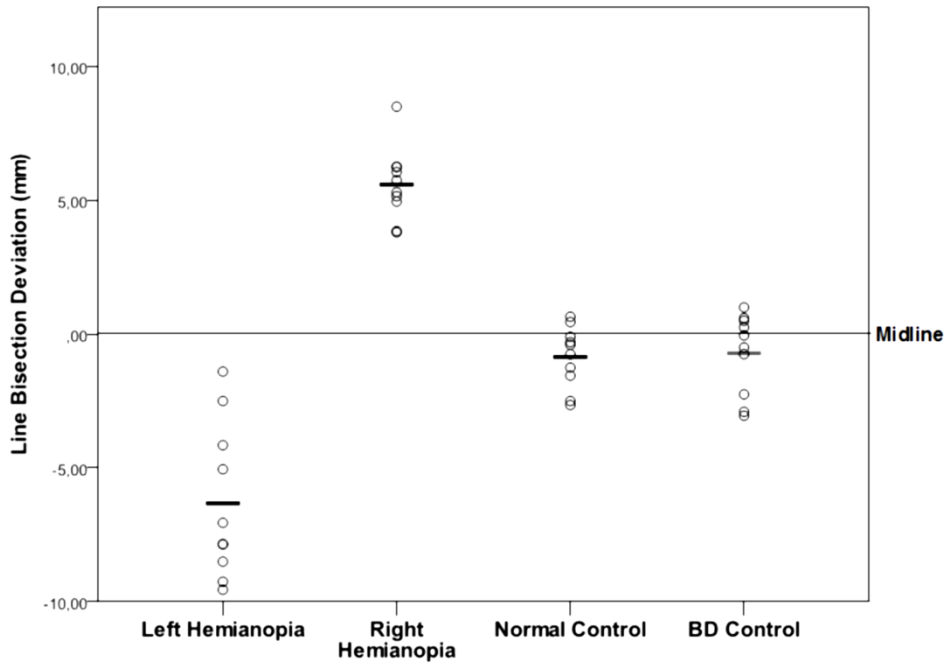

Fig. 7

Mean deviation (in mm) in horizontal line bisection in the four samples. Each circle represents one subject, horizontal black bars reflect the mean of every group. Positive values denote rightward deviations, negative values leftward deviations. Left hemianopia (N=10), right hemianopia (N=10), Normal Control (N=10) and Brain Damaged Control (BD).

2.2.3.5 Visual field sparing and size of the HLBE

There was no significant correlation between visual field sparing on the horizontal meridian in the blind field and the unsigned HLBE in the two hemianopic samples (Spearmans Rho= .04, p=0.87, two-tailed).

2.2.3.6 Position of the centre of the blind spot

To compare the mean positions of the centre of the blind spot between the experimental groups, ANOVAs and nonparametric tests were computed. There was no significant difference in the vertical position of the blind spot (Kruskal-Wallis-Test: X^2=3.476, df=3, p=.324), nor in the horizontal position of the blind spot (X^2=1.722, df=3, p=.632). Figure 8 displays all individual scores of the centre of the blind spot in all tested subjects. Note that the horizontal position of the blind spot centre lay within a small range of 13.5° to 17°

distance to the fixation point in the horizontal domain, which is in accord with previous studies where the blind spot was mapped in large samples of healthy subjects (Bixenman and von Noorden, 1982; Gradle and Meyer, 1929; Hopkins, 1941). Moreover, the vertical position of the blind spot centre was within normal limits (Bixenman and von Noorden, 1982), ruling out cyclorotation in most of the hemianopic patients. Two left HA patients showed an abnormal vertical position of their blind spot (one too high, the other too low in relation to the horizontal axis). However, vertical deviations of the blind spot are unlikely to influence *horizontal* line bisection.

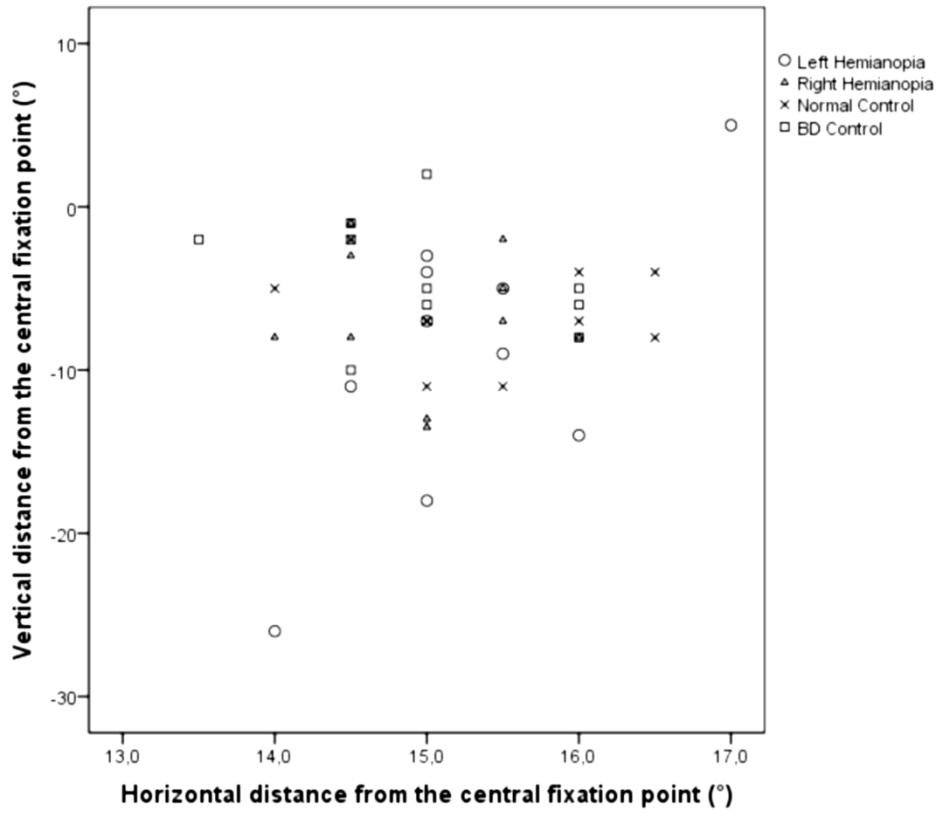

Fig. 8 Scatterplot of the horizontal and vertical position of the centre of the blind spot (ipsilesional eye) in 10 left hemianopic patients, 10 right hemianopic patients, 10 brain damaged control subjects and 10 normal controls subjects (1 brain damaged control subject excluded due to monocular viewing.

2.2.3.7 Interrelations of the position of the blind spot and the HLBE

There was no significant correlation of the position of the blind spot (horizontal deviation from fixation point) and the HLBE in the two hemianopic samples (Spearmans Rho; r=-0.16, p= 0.51).

2.2.3.8 Interrelations of the line bisection error and visual search field size

Fig. 10 shows a scatterplot of the relationship between the extent to which the hemianopic subjects were able to scan the blind field (visual search field) and their performance in the HLBE. Visual search field in the blind field did not differ significantly between the two hemianopic groups (mean left HA = 30.7°; mean right HA = 30.2°, Mann-Whitney-test: z=0, p=1.0, both lying just within the normal range). Saccadic search field size did not correlate significantly with the HLBE (Spearmans Rho = -0.11, p=0.66, two-tailed).

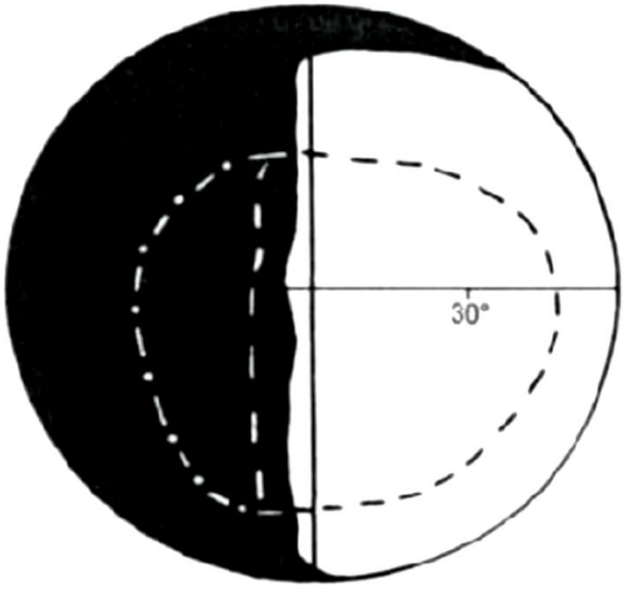

Figure 9: Illustration of the visual search field border in the blind field of two left hemianopic subjects (one with 10°, the other with 30°, indexed by the stippled lines). The search field border in the intact, right visual hemifield is 45°

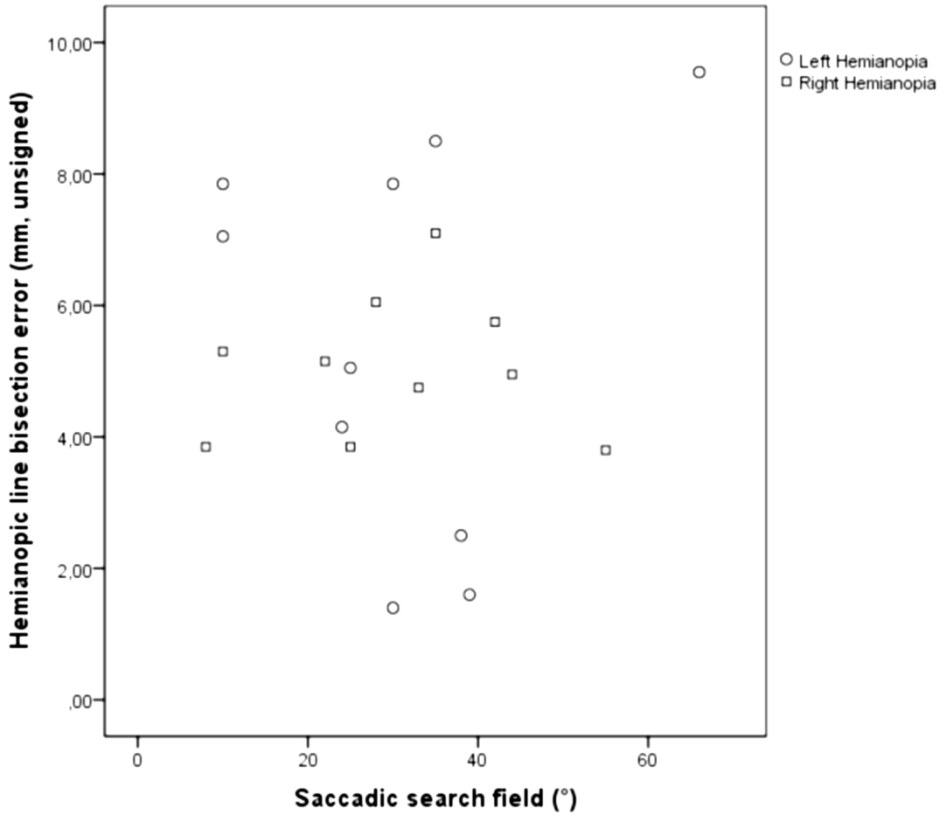

Figure 10: Scatterplot of the size of the hemianopic line bisection error (HLBE, unsigned errors in mm) and the size of the saccadic search field in the scotoma (in °) in 10 patients with left hemianopia and 10 patients with right hemianopia.

2.2.4 Discussion and conclusions

Our study revealed the following results: hemianopic patients do not show eccentric fixation as measured by blind spot mapping. Moreover, all hemianopic patients in our sample showed the typical contralesional HLBE, but this was not related to the position of the blind spot. Furthermore, the starting position in the experimental bisection task had virtually no effect at all on the HLBE, Hence, no spatial cueing effect was observed. As found in previous studies, visual field sparing was not related to the HLBE. In fact, 3 HA subjects with more than 12° field sparing also showed the HLBE. We will discuss these findings in detail below.

2.2.4.1 (Ec)-centric fixation

Significant eccentric fixation can be ruled out as an explanation for the spatial bias in horizontal line bisection in our rather chronic hemianopic subjects, as the horizontal and vertical positions of the blind spot were within normal limits in the majority of all tested subjects and agree with normative values of the position of the blind spot in healthy subjects (Bixenman and von Noorden, 1982; Gradle and Meyer, 1929; Hopkins, 1941). Moreover, blind spot coordinates did not correlate with the HLBE, and were not significantly different in the four samples studied. This also rules out a possible *cyclorotation* of the eyes in the majority of our HA patients, with the exception of 2 left HA patients who showed an abnormal *vertical* position of the blind spot, but normal *horizontal* position (Fig. 8). Since a horizontal shift of eye position would be of much greater importance as we examined *horizontal* line bisection, the vertical shifts in those 2 patients are most likely an associated, but unrelated phenomenon. As a caveat, it should be mentioned that although blind spot mapping provides a rather precise measure of (ec)centric fixation *during* the perimetric mapping procedure, subtle shifts of fixation might go undetected with this method. Moreover, we cannot exclude the possibility that although *static* eye position was normal in all hemianopic patients, *dynamic* eye position (i.e. during ocular scanning of the line) may have differentially contributed to the HLBE in the 2 hemianopic groups vs. the 2 non-hemianopic control samples.

In summary, there is no evidence supporting the notion that chronic hemianopic patients develop a new *pseudofovea* in the sense of an eccentric fixation towards their scotoma which in turn leads to the HLBE or is in any way related to this spatial error.

2.2.4.2 Spatial-Attentional Cueing

As the starting point of the slit which served to bisect the horizontal bar on the computer screen did not induce *any* effect on the HLBE, it was obviously irrelevant for all subjects. Hence, neither did patients with left or right HA benefit from such a spatial cue that must be attended because otherwise the subject cannot perform the bisection task, nor did their performance deteriorate in the opposite cue condition. This is in marked contrast to similar spatial cueing manipulations in patients with spatial neglect where a contralesional cue in

the neglected hemispace typically improves bisection performance while a cue on the ipsilesional side of the horizontal bar deteriorates bisection (Riddoch & Humphreys, 1983). It might be conjectured that our cueing procedure was simply ineffective in any subject not only in those with hemianopia, and therefore did not evoke a differential spatial bias. To test this hypothesis we investigated two patients with chronic leftsided visual neglect and leftward homonymous hemianopia and tested both in the very same horizontal bar bisection tasks as used in the present experiment. In patient 1, with a leftward slit position, line bisection was shifted towards the left side (-11.6 mm from the true centre), with a rightward cue position line bisection was shifted significantly towards the right (ipsilesional) side (+ 45.6 mm from the true centre). In patient 2, with a leftward slit position, line bisection was shifted slightly towards the right side (+6.1 mm from the true centre), with a rightward slit position line bisection was shifted markedly towards the right (ipsilesional) side (+ 16.0 mm from the true centre). These results clearly show that the cueing manipulation employed in our study can produce very profound effects on bisection performance, hence probably induced attentional shifts.

2.2.4.3 Oculomotor explanations of the HLBE

Some theories of the HLBE implicitly assume or explicitly state that the field defect itself causes the HLBE because the subject is never able to see the horizontal bar entirely, but has to scan it sequentially in parts by bringing his intact hemifield towards the blind side. While some studies with simulated hemianopia in healthy subjects (without brain damage) were able to induce a similar HLBE (Mitra et al, 2010), others did not find such effects (Schuett et al, 2009). We here observed a null relationship between the capacity to scan the blind field via saccadic eye movements and the HLBE (Fig.10). Poor oculomotor compensation of the field loss itself is a typical finding in acute hemianopia (Lane et al., 2010; Machner et al., 2009) and improves reliably during treatment of visual scanning and exploration (Pambakian et al., 2010), (Lane et al., 2010). In our sample of rather chronic hemianopic patients, *all 20 patients* showed a significant though admittedly small HLBE, irrespective of whether they scanned up to only 10°, 35 or even 66° in his/her blind field (see Table 2). In addition, 3 hemianopic patients had a significant contralesional HLBE despite a visual field sparing of at least 12° or even more on the blind side. Put differently:

these patients could have seen the horizontal line entirely with their intact hemifield and the spared visual field on the blind side, but still showed the HLBE. While these observations – in our view - render a pure oculomotor explanation of the HLBE in our mostly chronic patients unlikely, we must admit that we do not know how these 3 patients would have bisected *very long lines* that could not be seen entirely with the remaining visual field on the blind side. Potentially, with such long lines a similar compensatory scanning pattern towards the part of the line presented in the blind field would have emerged as with shorter lines in those patients who cannot see the line entirely because of a small visual field sparing. According to this scenario, the mechanism(s) involved in the HLBE might in part depend on the horizontal spatial extent of the perceptual object that is to be bisected *and* the size of the scotoma or the residual field sparing available for performing this task. Moreover, problems of oculomotor scanning may very likely contribute to the HLBE in *acute* hemianopia (cf Machner et al., 2009) when patients try to adapt to the sudden field loss.

As a caveat we have to admit that our procedure of measuring the saccadic search field – though sensitive and well suited to follow oculomotor compensation in hemianopia throughout therapy (Kerkhoff et al, 1992, 1994) may have been too insensitive to detect subtle oculomotor discrepancies between hemianopic patients *with* a marked HLBE and those with a small HLBE. Anyway, we find it remarkable that hemianopic subjects who are well able to scan up to 50 or 60° in their blind field (see Fig. 9 & 10) may nevertheless show a considerable problem in bisecting horizontal lines.

2.2.4.4 Alternative explanations of the HLBE

While our results suggest that neither eccentric fixation, nor spatial cueing nor oculomotor deficits are likely explanations of the contralesional spatial bias observed here in *chronic* hemianopic patients – some 9-12 months after manifestation of their hemianopia – alternative explanations of this phenomenon have been suggested (for a more detailed discussion see Kerkhoff and Schenk, (2011). The attention-account suggested by Barton and Black (1998) – as mentioned earlier - and more recently elaborated by Mitra and co-workers (Mitra et al., 2010) claims that the HLBE is a direct consequence of the field defect itself, because hemianopic patients are forced to view the line in just one hemifield,

just as normal subjects with virtual hemianopia are. This may lead to an asymmetrical distortion of the spatial representation of the line and consequently produce the well-known bias in patients' bisection performance. Barton & Black (1998) also considered a more indirect link between HLBE and visual field defects, arguing that the visual field loss in one hemifield leads to a strategic shift of attention into the contralesional hemispace, thereby producing the line-bisection bias. This hypothesis is supported by eye-movement recordings *during* line-bisection in hemianopic patients, which show that the fixation pattern is shifted towards the hemianopic side (Barton et al., 1998) (Ishiai et al., 1989) and restates an earlier hypothesis proposed by (Williams and Gassel, 1962). In contrast, the lesion account (Zihl et al., 2009) rejects this argumentation and states that the HLBE results from occipito-temporal brain damage and is therefore relatively independent from visual field sparing. According to this account, the HLBE represents an independent visuospatial deficit in hemianopia similar to those in reading (Spitzyna et al., 2007) or visual scanning (Mannan et al., 2010). Recent evidence (Baier et al., 2010) strengthened the anatomical explanation of the HLBE as a direct consequence of lesions to the lingual gyrus and cuneus. We have argued recently (Kerkhoff and Schenk, 2011) that - in our view - it is premature to finish the discussion about the sources of the HLBE by deciding in favor or against one of these hypotheses, because many issues are still unresolved.

2.2.4.5 Unsettled issues

One is the frequent observation that especially patients with left HA and to a smaller extent also those with right HA report problems like striking against door frames or boards and failure to take notice of people passing by in the blind hemifield (Gassel & Williams, 1963, Kerkhoff et al, 1994). To our knowledge, no one has correlated these observations with the HLBE. Second, hemianopic patients often report feelings of dizziness and show postural deficits, confirmed by posturographic measurements (Rondot et al, 1992), which showed a shift of the centre of pressure during standing towards the blind side – just as in line bisection. Hence, it appears that the HLBE not only affects perception or manual line bisection, but obviously produces more visuomotor deficits which may be quite relevant in the clinical setting and in daily life.

A recent study (Hesse et al., 2012) investigated the effects of V1-damage and subsequent hemianopia (in 12 patients) on a set of visuospatial and visuomotor tasks which all had in common that the patients had to indicate verbally the midline or point to a midline position of a distance or a line. Hesse and coworkers replicated the typical HLBE in their verbal midline task, but also found a nearly identical contralesional HLBE in their second task (pointing to a midline position on a horizontal line shown on a touchscreen) and their third (an obstacle avoidance task requiring a pointing response to the midline of a horizontal distance). Taken together, this study revealed that the contralesional HLBE in hemianopia is very robust, as it was present in perception *and* action tasks. No differential influence of visual field sparing on the spatial error was noted in this study (field sparing ranged from 0-4° in all patients). This study shows that the HLBE has widespread effects on the perception-action cycle in hemianopia.

2.2.4.6 Conclusions

We conclude, that neither eccentric fixation nor the degree of oculomotor compensation of the field loss itself are sufficient explanations for the contralesional spatial bias (HLBE) observed in patients with *chronic* hemianopia. Moreover, spatial-attentional cueing was ineffective in modulating this bias, and therefore attentional impairments or adaptations appear unlikely explanations of the HLBE in our HA sample. However, both the attentional-cueing and oculomotor compensation account requires further analyses in subsequent studies.

2.3 Study III

Does spatial cueing affect line bisection in chronic hemianopia?

Kuhn, C., Rosenthal, A., Bublak, P., Grotemeyer, K.H., Reinhart, S. & Kerkhoff, G. (2012). *Neuropychologia*, 50(7), 1656-1662.

2.3.1 Introduction and rationale

Patients with homonymous hemianopia often show a contralesional shift towards their blind field when bisecting horizontal lines ("hemianopic line bisection error", HLBE). The reasons for this spatial bias are not well understood and debated. Cueing of spatial attention modulates line bisection significantly in patients with visuospatial neglect. Moreover, recent evidence showed that attention training significantly improves deficits of visual search in hemianopia. Here, we tested in 20 patients with chronic homonymous hemianopia (10 left-sided, 10 right-sided) without visual neglect, 10 healthy control subjects, 10 neurological control patients, and 3 patients with left visuospatial neglect and leftsided hemianopia whether spatial cueing influences the HLBE. Subjects indicated verbally the midpoint of horizontal lines in a computerized line bisection task under four experimental cue positions (cue far left, mid-left, mid-right or far-right within the horizontal line). All 20 hemianopic patients showed the typical HLBE towards their blind field, while the two control samples showed only a small but significant leftward shift (pseudoneglect). None of the 4 cueing manipulations had a significant effect on the HLBE in the hemianopic patients. Moreover, no differential effects of cueing on line bisection results were obtained when analysed in lesion subgroups of hemianopic patients with circumscribed occipital lesions (N=8) as contrasted with patients having more extended (occipito-temporal or temporal) lesions (N=12). This null-effect contrasts with marked cueing effects observed in 3 neglect patients with left hemianopia in the same tasks, showing the principal efficacy of our cueing manipulation. These results argue against attentional explanations of the HLBE.

Unilateral lesions of the posterior visual pathways in the human brain often cause contralateral homonymous visual field defects (Miller, Newman, Biousse, & Kerrison, 2008). Typically, patients with such scotomas show a variety of associated disorders (for review see (Lane, Smith, & Schenk, 2008), including hemianopic alexia (Spitzyna et al., 2007; Schuett, 2009; Kerkhoff, Münbinger, Eberle-Strauss, & Stögerer, 1992; Pflugshaupt et al., 2009), inefficient visual search in the scotoma (Machner et al., 2009; Lane, Smith, Ellison, & Schenk, 2010; Keller, Lefin-Rank, & G., 2010) and a peculiar spatial bias towards their blind field when bisecting long horizontal lines or indicating their subjective visual straight ahead. Although completely forgotten for several decades (Kerkhoff & Bucher, 2008) this spatial bias is well known as the hemianopic line bisection error (further termed HLBE) since Axenfeld´s seminal description in 1894 (Axenfeld, 1894). Recent investigations have largely replicated and extended these early findings (Kerkhoff & Schenk, 2011; Schuett, Dauner, & Zihl, 2010; Zihl, Sämann, Schenk, Schuett, & Dauner, 2009; Doricchi et al., 2005). Besides *horizontal* deviations in line bisection (Hausmann, Waldie, Allison, & Corballis, 2003; Zihl et al., 2009; Doricchi et al., 2005; Barton & Black, 1998) or in the visual subjective straight ahead orientation (Ferber & Karnath, 1999), vertical shifts in altitudinal hemianopia (Kerkhoff, 1993), or oblique shifts of the subjective visual straight ahead in homonymous quadrantanopia (Kuhn, Heywood, & Kerkhoff, 2010) were found. This *contralesional* spatial error contrasts with the well-known *ipsilesional* spatial error in the same tasks in patients with visuospatial neglect (Halligan, Manning, & Marshall, 1990); (Schindler & Kerkhoff, 2004).

Despite this convergence of results demonstrating the *existence* of a contralesional spatial-perceptual bias in different types of heminopia (HA) or other types of visual field defects, the precise reason(s) for its occurrence are less clear and currently debated (Kerkhoff & Schenk, 2011). Early researchers of the HLBE advanced several theoretical explanations of this error (Kerkhoff & Bucher, 2008). One prominent account surmised that the HLBE towards the blind field reflects a kind of adaptive, oculomotor strategy which helps the patient to orient his eyes and attention further towards the blind field, which in turn might improve visual orientation and reduce the typical visual complications such as bumping into obstacles or disregarding persons on the blind side (Gassel & Williams, 1963). A recent study (Machner et al, 2009) reported no contralesional HLBE in acute HA and speculated that the HLBE in chronic HA thus may result from slow,

strategic, attentional adaptation to the scotoma. However, another recent study found no difference in the amount of the HLBE in acute versus chronic HA, and found in nearly all patients the typical contralesional error which was causally related to lesions of the lingual gyrus and cuneus (Baier et al, 2010). Their data do not support an interpretation of the HLBE as an attentional and oculomotor adaptation to the scotoma, but rather interpret it as a direct consequence of the extrastriate cortical lesion.

If the HLBE reflects or facilitates attentive orienting towards the blind field, experimental manipulations which direct spatial attention to or away from the blind side should modulate the HLBE in HA, just as they have been shown to modulate the ipsilesional line bisection error in patients with visuospatial neglect (Riddoch & Humphreys, 1983; Butter, Kirsch, & Reeves, 1990, Lin, Cermak, Kinsbourne, & Trombly, 1996). To our knowledge, no study so far has investigated the role of spatial cueing in the HLBE. We therefore investigated in the present study in matched samples of rather chronic patients with left versus right-sided HA – all without unilateral visual neglect - , control patients with acquired brain damage but without HA or neglect, and healthy control subjects whether spatial cueing modulates the HLBE. In addition we tested the principal efficacy of our spatial cueing paradigm in 3 patients with leftsided neglect and leftsided hemianopia.

2.3.2 Methods

2.3.2.1 Patients and control subjects

20 patients with perimetrically established unilateral, homonymous HA following unilateral posterior cerebral lesions (10 left-sided, 10 right-sided; see Table 4) and 10 patients with unilateral or diffuse-disseminated brain lesions, but with perimetrically intact visual fields were tested (further termed Brain Damaged control patients; Table 4). Stroke was the most frequent aetiology in the HA sample (n=17, 85 %), followed by tumour operated (n=2, 10%) and closed head trauma (n=1, 5%). In addition, 10 healthy, dominantly right-handed (handedness-quotient of +100 in all cases) control subjects (8 male, 2 female, mean age 50.5 years; range 22-70) were recruited.

None of the healthy control subjects had evidence of ophthalmological, neurological or psychiatric disease. All had perimetrically normal visual fields, and a mean visual acuity of 0.98 (mean, range 0.7-1.2) for the near visual distance (0.4 m) in a standardized letter acuity chart.

In addition, three patients with leftsided spatial neglect and leftsided hemianopia after a right middle cerebral artery stroke (9, 11 and 12 months after stroke, respectively) were tested. All three patients were righthanded (+100 laterality quotient) and showed symptoms of leftsided visual neglect in several of the 5 neglect screening tests. In manual horizontal line bisection, 2 patients showed a rightward shift: Patient 1: + 19 mm, Patient 2: + 10 mm. Patient 3 showed a leftward shift: -6 mm away from the true centre. In number cancellation all 3 patients omitted targets on the left side and to a smaller degree also on the right side (Patient 1: 8 left vs. 3 right), Patient 2: 3 vs. 1; Patient 3: 2 vs. 1). Patient 1 showed leftward omissions when drawing a clock face from memory, patient 2 drew a normal clock face from memory, patient 3 showed distortions of the left side of the clock face and incorrect placement of the numerals on the left side of the clock face. Patient 1 and 2 showed signs of leftsided neglect in figure copying, patient 3 not. Patient 1 showed 11 omissions in the indented reading test, patient 3 showed 2 leftsided omissions, while patient 2 scored normally in the reading task. Visual perimetry revealed leftsided HA in all three cases (field sparing on the horizontal meridian: 4°, 6° and 2°, respectively). Visual search field was 16° in patient 1, and 33° in patient 2 in the left (blind) hemifield (search field could not be determined in patient 3 due to use of an *automatic* perimeter not allowing the *manual* measurement of the search field). In sum, all three patients had chronic leftsided HA plus leftsided visuospatial neglect.

All HA patients received visual exploration training (Kerkhoff et al., 1994) as well as hemianopic reading training (if they showed hemianopic alexia, (Kerkhoff & Marquardt, 2009) over a time period of 4-6 weeks. All investigations of the current study were carried out *before* these treatments started, so that the treatments could have no differential effect on the current results. Brain damaged control patients did not receive visual treatments and were enrolled in the study before receiving any other neuropsychological treatment.

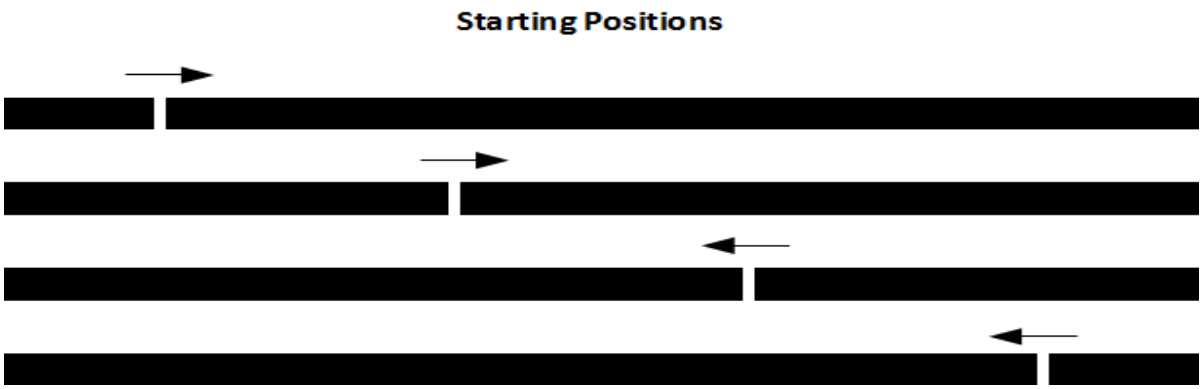

Figure 10: Schematic illustration of the 4 line bisection tasks. Four different starting positions of the slit in the line bisection task (far-left, mid-left, mid-right, far-right) were used to manipulate spatial attention. The arrows depict the direction of movement of the bisection slit. Note that the bisection task can only be solved when the subject attends the slit that bisects the horizontal bar.

2.3.2.2. Clinical-Neuropsychological tests

Handedness was determined in all subjects with the German version of the Edinburgh handedness inventory (Salmaso & Longoni, 1985) which measures hand preference. This is expressed as a laterality quotient ranging from -100 (=strongly left-handed) over 0 (=ambidextrous) to +100 (=strongly right-handed; results see Table 4). Visual letter acuity was measured separately for each eye with standardized, high-contrast letter charts (Fronhäuser, München, Germany) for the near (0.4 m) viewing distance in all 4 samples. Binocular visual fields were mapped with a Tübingen perimeter in all patients (for a detailed description see (Kuhn et al., 2010) results see Table 4). In short, dynamic visual perimetry was performed with a circular white target (luminance: 102 cd/m^2; size: 1.02°) using a Tübingen bowl perimeter in a completely dark room. With the same perimeter, the extent of the visual search field - a measure of oculomotor capacity in the blind field – was measured (details in (Kerkhoff, Münbinger, & Meier, 1994). The subject was instructed to search with saccadic eye movements for a circular white target (size: 1.02°, luminance: 102 cd/m^2) that was moved by the perimetrist along every meridian from the periphery to the centre with a speed of 2°/sec. The sequence of the meridians tested was random. The patient presses the response key as soon as she/he detects the target. This position is scored as the eccentricity of the search field (in °).

Here, we indicate the average of the search field of all 6 meridians lying in the *blind* hemifield; the lower normal cutoff is 30° (Kerkhoff et al., 1994).

Five conventional visual neglect tests – comparable to the Behavioural Inattention Test (Wilson, Cockburn, & Halligan, 1987) - were performed to rule out visual neglect in our HA samples and document visual neglect in the 3 additonal patients with neglect: horizontal line bisection of a 20 x 0.2 cm black line on a white sheet of paper; number cancellation (30 targets among 150 distracters, presented on a 29.7 x 21 cm large white paper), drawing of a clock face from memory, copying 3 geometrical figures (a star, a daisy, a face; each on a different sheet of paper) and an indented reading test of 180 words. Neglect was diagnosed when the truncation midline in bisection deviated more than 5 mm to the *ipsilesional* side (Kerkhoff, 1993), when more than 1 target was omitted on one side in number cancellation, when numerals were omitted or misplaced on the left side of the clock face test, or when the subject committed more than 2 reading errors in the indented reading test (Reinhart, Schindler, & Kerkhoff, 2011). None of the 3 patient groups (HA samples, BD control group showed any signs of visual neglect in any of the 5 neglect screening tests.

Visual perimetry and visual search field testing as well as the experimental line bisection testing were performed in a totally darkened room (< 10 Lux room lighting), the only visible stimulus in perimetry and search field testing was the background illumination of the perimeter (3.2 cd/m^2) and the test stimulus. In line bisection tests the only visible stimulus was the horizontal, white bar on the black computer screen. All other (screening) tests took place in a day-lit room (mean lighting: approximately 400 Lux).

2.3.2.3 Computerized Horizontal Line Bisection Task

Subjects were placed in front of a computer screen (17´´) in a distance of 0.45 m. The head was positioned in a head- and chinrest mounted on a table in front of the screen to prevent head movements during testing. On the screen a white horizontal bar (160 x 10 mm, luminance: 100 cd/m^2) appeared centrally on the black screen. The bar contained a vertical slit (size: 5 x 10 mm) that appeared – in different experimental conditions - either on the far left end of the bar, in a mid-left position, in a right-mid position or on the far-right position of the bar (Fig. 11). The subject was asked to determine verbally when the slit was

exactly in the centre of the horizontal bar. To this purpose the examiner moved the slit via the software program (Kerkhoff & Marquardt, 2004) in steps of 1 mm slowly towards the other side of the bar until the subject indicated that the slit was exactly in the middle of it. To ensure patients were fixating the gap during each bisection trial the experimenter asked every subject when starting a bisection trial whether he/she could see the gap on the left/right side of the bar and and how it changed position according to the verbal commands of the subject to the experimenter. The experimenter checked regularly when moving the gap along the bar whether the subject re-fixated the new position of the gap within the bar. However, no eye tracking control was adapted to measure quantitatively whether the subject´s eye in fact fixated the gap.

Ten trials were performed within each of the 4 cueing tasks; 5 trials were performed en block with the gap starting from the left side and 5 trials were performed en block with the gap starting from the right side of the bar. This resulted in a total of 10 trials per cueing task. The sequence of the blocks was counterbalanced. Constant errors were computed using the method of limits by special software (Kerkhoff & Marquardt, 1998; Kerkhoff & Marquardt, 2004) between the objective centre of the bar and the mean position of the slit as determined by the subject. No motor component was involved in this bisection task on the subject´s side, nor was there any time limit for the subjects.

Table 4
Patient data: L1-L10: left Homonymous Hemianopia; R1-R10: Right Homonymous Hemianopia;
C1-C10: Brain damaged control patients

No.	Age (yrs)/ Sex	Aetiology TSL (months)	Lesion side localization	Visual acuity near LE/RE (%)	Visual field sparing (°)	Visual search field (°)	Handedness
L1	69/f	CVI/120	R-occ	50/60	2	35	+100
L2	40/f	CVI/10	R-occ	100/100	14	66	+100
L3	71/m	CVI/24	R-occ	90/-	4	15	+100
L4	63/m	CVI/13	R-occ	60/50	2	25	+100
L5	32/f	CVI/9	R-occ-temp	60/50	1	30	+100
L6	31/f	CVI/2	R-par-temp	125/125	1	10	+100
L7	33/m	CVI/168	R-occ-temp	100/100	2	10	+100
L8	56/m	SHT/5	R-par-temp	90/50	4	42	+100
L9	32/m	CVI/96	R-temp	90/90	1	30	+100
L10	32/m	CVI/48	R-occ-temp	100/100	2	38	+100
Mean	45.9/-	-/49.5 **Md:** 13	---	86.5/80.6	3.3° **Md**: 2	30.1	+100
No.	**Age (yrs)/ Sex**	**Aetiology TSL (months)**	**Lesion side localization**	**Visual acuity near LE/RE (%)**	**Visual field sparing (°)**	**Visual search field (°)**	**Handedness**
R1	44/f	CVI/15	L-occ-temp	70/70	5	22	+33.3
R2	66/m	CVI/4	L-occ-temp	80/80	15	42	+100
R3	42/m	CVI/36	L-occ-temp	80/80	20	55	+60
R4	48/m	CVI/38	L-occ-temp	80/80	3	44	+100
R5	44/m	Tu/11	L-occ-temp	80/80	5	34	+100
R6	58/m	CVI/7	L-occ	90/90	4	28	+100
R7	33/m	Tu/19	L-par-occ	100/100	6	45	+100
R8	69/m	CVI/3	L-occ	80/70	2	8	+100
R9	62/m	CVI/17	L-occ	100/60	5	10	+100
R10	39/f	CVI/3	L-occ	125/30	3	26	+100
Mean	50.5/-	-/15.3 **Md:**9	---	88.5/74.0	6.8° **Md:** 5	31.4	+89.3
No.	**Age (yrs)/ Sex**	**Aetiology TSL (months)**	**Lesion side localization**	**Visual acuity near LE/RE (%)**	**Visual field sparing (°)**	**Visual search field (°)**	**Handedness**
C1	46/m	Enceph./4	L-temp	100/100	---	---	+100
C2	55/m	Sepsis/10	diffuse	120/120	---	---	+100
C3	49/m	CVI/10	diffuse	90/90	---	---	+100
C4	55/m	CVI/50	L-BG	-/63	---	---	+100
C5	47/m	CVI/15	L-BG	100/100	---	---	+100
C6	63/m	CVI/2	L-temp	120/120	---	---	+100
C7	59/m	CVI/3	R-front-temp	100/100	---	---	+100
C8	48/m	CVI/8	L-temp	100/80	---	---	+100
C9	63/f	CHI/34	diffuse	100/70	---	---	+100
C10	42/f	CVI/14	L-temp	100/100	---	---	+100
Mean	52.7/-	-/15.0 **Md:**10	---	103.3/94.3			+100

Legend: **m/f:** male/female; **LE/RE**: left/right eye; **L/R:** left/right; **Enceph**: encephalitis; **BG**: basal ganglia, **Tu**: tumour operated; **CVI:** cerebrovascular insult; **CHI:** closed head injury; **TSL**: time since lesion onset in months; **L/R:** left/right; o**cc**: occipital, **par**: parietal, t**emp**: temporal.

2.3.3. Results

2.3.3.1. Comparison of the samples

Statistical comparisons revealed that neither handedness ([F(3, 36) = 1.47; p = 0.24]), nor age ([F(3, 18.78) = 1.22; p = 0.33]), nor gender [X^2 (3, n=40) = 2.88, p=0.41] were significantly different between the four samples. Visual acuities for the near viewing distance (0.4m) were examined separately for the left and the right eyes. There were no significant differences between the three patient groups ([F(2, 26) = 2.59; p = 0.9] for the left eye; [F(2, 26) = 2.16; p = 0.14] for the right eye).

Moreover, the three patient groups did not differ significantly regarding time since lesion (median left HA = 18.50 months; median right HA = 13.00 months, median control patients= 10 months; [F(2, 16.12) = 1.62; p = 0.23]).

2.3.3.2. Visual field sparing and saccadic search field

Both hemianopia (HA) samples did not differ significantly from each other in visual field sparing (mean left HA = 3.3°; mean right HA = 6.8°; T(18)= -1.57, p= 0.135). One out of ten leftsided HA patients showed a visual field sparing of 14°. Among the rightsided HA sample one patient had a field-sparing of 15°, the second of 20°. Visual search field in the blind field did not differ significantly between the two HA groups (mean left HA = 30.1°; mean right HA = 31.4°, T(18)=-0.18, p=0.86). Saccadic search field did not correlate significantly with the HLBE (Spearman correlations: Rho: -0.072, p>0.05, two-tailed).

3.3. Spatial cueing direction in hemianopic patients and control subjects

The vertical slit was moved by the experimenter towards the middle of the bar, starting at different positions (far-left, mid-left, mid-right, far-right). To examine if there was a possible "cueing" effect due to these starting positions, an ANOVA with the factors group (HA left, HA right, normal control, and BD control) and starting position was computed. There was no main effect of starting position [F(3, 108)=1.76, p=0.16] and also no

significant group × starting position interaction [F(9, 108)= 0.92, p=0.51]. The significant effect of group [F(3, 36)= 61.58, p<0.001] indicated the expected line bisection deviation error of HA patients to the *contralesional*, blind field (leftwards in left HA, rightwards in right HA; Fig. 2). Subsequent comparisons revealed significant differences between the HA groups and the two control groups [left HA: T(36) = -7.46, p < 0.001; right HA: T(36)= 8.23, p < 0.001], but no significant difference between the two control groups (mean difference = 0.015 mm, p = 0.948). Both control groups showed the expected pseudoneglect [normal control: mean leftward shift = -2.92 mm, T(9) = -1.98, p = 0.039; BD control: mean leftward shift = -2.98 mm, T(9) = -1.75, p = 0.055, see Fig. 12].

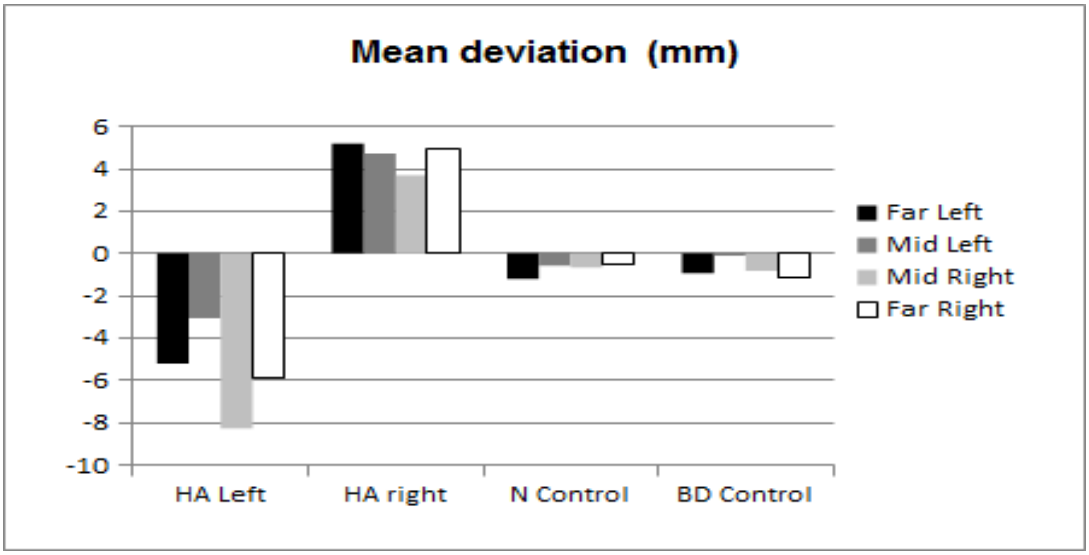

Fig. 12:

Mean deviations (signed errors, in mm) of the four experimental groups in the 4 line bisection tasks. Negative or positive deviations illustrate leftward or rightward deviations from the physical midline of the line. HA left/right: left vs. rightsided hemianopia; N Control/BD Control: normal control subjects vs. brain damaged control subjects.

2.3.3.4. Spatial cueing in relation to lesion anatomy

Although we found no evidence of spatial cueing in line bisection in our hemianopic patients (see *2.3.3.3* above), this effect might theoretically be due to a mixture of a subgroup of patients who indeed may have responded to cueing and those who did not respond. One interesting modulating variable in this context that may have influenced cueing differentially is lesion anatomy. As we know that cueing in neglect patients with temporo-parietal lesions is very effective it might be hypothesized that cueing might also work better in HA patients with lesions beyond the occipital lobe, i.e. temporo-occipital lesions. As some of our hemianopic patients had pure occipital lesions while others had lesions including occipital brain areas but extending beyond the occipital lobe (in most cases into the temporal cortex), the nonsignificant effect of spatial cueing thus may have been due to a mixture of these two subgroups. To examine whether the bisection errors were different in these two subgroups (irrespective of the side of hemianopia), an ANOVA with the factors group (occipital lesion versus extended lesion) and starting position (far-left, mid-left, mid-right, far-right) was computed on the unsigned HLBE. Again, there was no main effect of group [$F(1, 108)=0.166$, $p=0.689$], no main effect of starting position [$F(3, 54)=0.142$, $p=0.884$], and no significant group × starting point interaction [$F(3, 54)=0.668$, $p=0.530$]. Hence, no differential influence of lesion anatomy was found on the HLBE under the four different cueing conditions. Fig. 14 summarizes the results.

2.3.3.5 Spatial cueing direction in neglect patients

The single data from the 3 neglect patients were collapsed for each task and analysed with nonparametric statistics across the 4 spatial cueing task conditions. A Friedman-Test revealed a highly significant difference between the 4 task conditions ($X^2=28.45$, $df=3$, $p<0.001$). Subsequent paired comparisons with Wilcoxon-Tests revealed significant differences between the following task/cueing conditions: Far-Left vs. Mid-Right ($z=-3.297$, $p<0.001$); Far-Left vs. Far-Right ($z=-3.408$, $p<0.001$); Far-Right vs. Mid-Right ($z=-2.728$, $p<0.001$), and Mid-Left vs. Far-Right ($z=-3.448$, $p<0.001$).

All other comparisons did not reach statistical significance (largest z-value: -1.023, smallest p=0.306). In summary, four of the 6 possible statistical comparisons between the 4 spatial cueing conditions revealed a highly significant effect of the cue position on line bisection performance.

In general, leftward cue positions were associated with a leftward shift in line bisection, whereas more rightward cue positions led to a more rightward shift in line bisection as compared to the more leftward starting positions of the cue (see Fig. 13, averaged results on the right side).

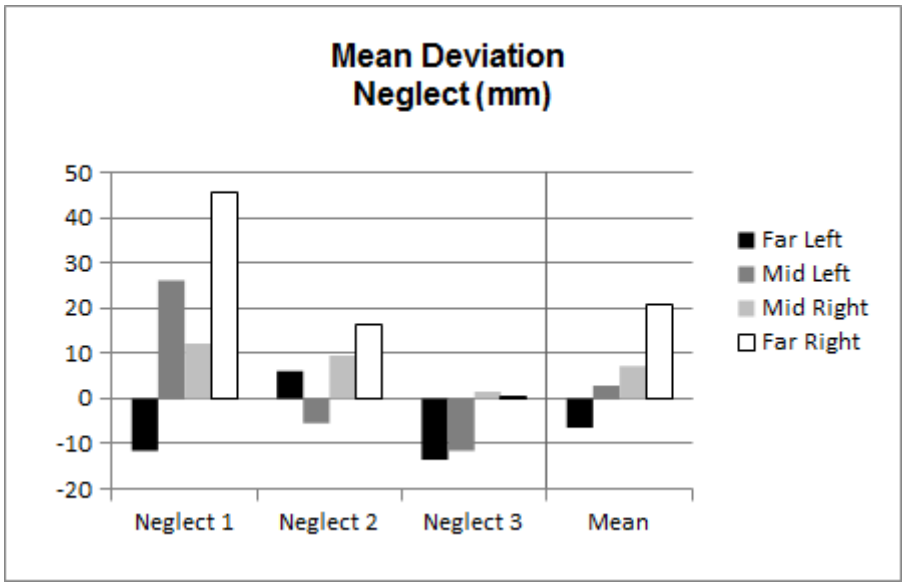

Fig. 13:
Mean deviations of 3 patients with leftsided visual neglect and leftsided hemianopia in the line bisection task under four different cue conditions (see Fig. 10). Note the different scaling of the y-axis as compared to figure 11, due to the large cueing effects in the 3 patients. Same convention of deviations as in Fig. 12

2.3.4. Discussion

Our study revealed clearly, that 4 different manipulations of spatial cueing had no significant effect at all on the HLBE. As the starting point of the slit which served to bisect the horizontal bar on the computer screen did not induce *any* effect on the HLBE, it was obviously irrelevant. Hence, neither did patients with left or right HA benefit from such a spatial cue that must be attended because otherwise the subject cannot perform the bisection task, nor did their performance deteriorate in the opposite cue condition. It might be conjectured that this was simply because our spatial cueing manipulation was ineffective. However, the very same manipulation revealed significant spatial cueing effects in the 3 patients with leftsided HA and left visuospatial neglect (Fig. 13). These cueing effects were significant for 4 out of 6 possible comparisons between the 4 cueing conditions, thus showing a strong effect of the slit position on bisection performance despite the small group of neglect patients. In general, the final bisection performance revealed a clear covariation with the initial starting position of the slit. Put differently: the more leftward the cue position, the more leftward the bisection and vice versa. These observed spatial cueing effects in our 3 neglect patients are largely compatible with earlier findings – though achieved with different experimental manipulations - showing that a leftsided (contralesional) cue in the neglected hemispace (a letter, a hand movement or a moving stimulus, see below) typically shifts bisection towards the cue while a cue on the right (ipsilesional) side of the horizontal bar shifts bisection towards this cue was either ineffective or even deteriorated performance (Riddoch & Humphreys, 1983; (Butter et al., 1990; Lin et al., 1996).

Our null-finding of spatial cueing in chronic HA (without neglect) may be surprising at first glance given that repetitive visual attention training is clearly effective as a treatment for the visual search disorder of HA patients (Lane et al., 2010), and in light of the robust effects of the same spatial-attentional cues on line bisection in visual neglect. However, a recent study by Baier et al (2010) found the HLBE in acute and chronic HA indicating no emergence as a kind of compensatory behaviour that facilitates attentive orienting to the blind field. Together, their and the current findings suggest that the HLBE in chronic HA is not the consequence of hyperattention to the blind or hypoattention to the intact visual field.

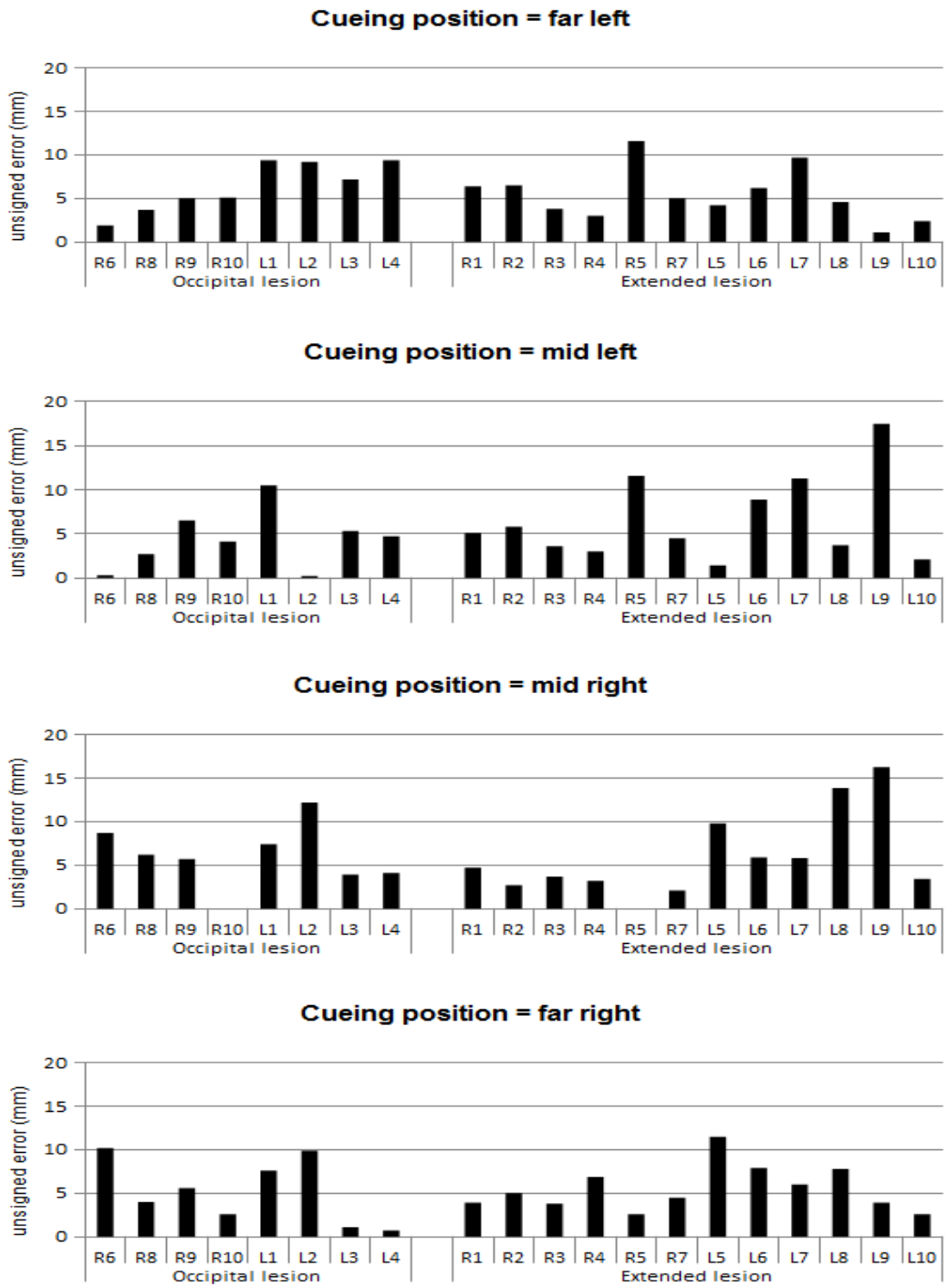

Fig. 14: Mean unsigned line bisection errors (in mm) in the 4 spatial cueing conditions during line bisection (see Fig. 10), shown separately for patients with pure occipital lesions vs. patients with lesions extending beyond the occipital lobe (extended lesions). Note that left and right hemianopic patients were collapsed into the two lesion subgroups irrespective of the side of hemianopia. Positive deviations indicate bisection errors toward the blind field.

Rather, the lesion data of Baier et al (2010) and Zihl et al. (2009) suggest that the HLBE is unlikely of attentive origin, but reflects a kind of spatial-perceptual error to the contralesional side, that emanates early in the course of hemianopia and may persist for a long time. Moreover, the comparable size of the HLBE in acute and chronic HA patients in the Baier et al. (2010) study argues against the gradual development of the HLBE in terms of a compensatory phenomenon. Furthermore, the null-effect of spatial cueing as analysed in different lesion subgroups of our hemianopic patients suggests that the HLBE is a robust phenomenon that is not as easily modulated as its counterpart in patients with leftsided hemianopia plus neglect (as shown in Fig. 13 of our study). Taken together, all these accumulated findings render an explanation of the HLBE in terms of facilitating attentive orienting towards the blind field unlikely.

Obviously, the HLBE does not "serve" a better compensation of the field loss as implicitly assumed in early theories (Gassel & Williams, 1963) or more explicitly stated in recent explanations (Mitra, Abegg, Viswanathan, & Barton, 2010). More specifically, according to the current results spatial attention does not seem to play a major role in the maintenance of the HLBE in c*hronic* hemianopia. Rather, the HLBE represents a type of visuospatial disturbance that immediately follows after lesion to some extrastriate cortical areas.

Finally, a very early account of the HLBE can be rejected as well. The german vision researcher W. Poppelreuter (Poppelreuter, 1922) suggested that HA patients develop a new "pseudofovea" located some degrees in the contralesional, blind field. Although he did – to our knowledge – not explicitly state that the HLBE and the "pseudo-fovea" might be connected as both represent a contralesional spatial shift towards the scotoma, it is tempting to assume that both might be co-related. More recent studies (Trauzettel-Klosinski, 1997) have supported this notion with their finding of a small fixational shift to the blind field which according to their interpretation facilitates reading. We recently tested the eccentric-fixation hypothesis (Poppelreuter, 1922) as a potential explanation of the HLBE explicitly by blind spot mapping of the ipsilesional eye in 20 HA patients, 10 nonhemianopic, but brain-damaged control patients and 10 healthy individuals (Kuhn et al., 2012). Importantly, the position of the blind spot was in the normal range in 38 of 40 tested subjects, did not differ significantly between hemianopic and nonhemianopic groups, and did not correlate significantly with the HLBE which was present in all 20 HA

patients. Moreover, the HLBE showed no significant correlation to the capacity of the HA subjects to explore their blind field with scanning eye movements ("visual search field") which might have been expected if the HLBE reflects a compensatory orienting of eye movements to blind field. Together, these recent results show that eccentric fixation plays no major role in the emergence of the HLBE. The same conclusion was reached for the contralesonal, oblique error in the subjective visual straight ahead observed in 15 nonneglecting patients with homonymous quadranopia, which was not accompanied by any abnormality of horizontal or vertical eye position as determined by blind spot mapping (Kuhn et al, 2010). Moreover, visual scanning capacity in the blind field and the size of the HLBE towards the blind field are unrelated phenomena, suggesting that the HLBE represents an independent, third feature of HA patients besides their well-established visual exploration deficits and hemianopic alexia.

Despite our clear results, some caveats have to be mentioned. Firstly, other types of spatial cueing, i.e. local or global *visual motion* cues, which effectively modulate line bisection and other visuospatial deficits in patients with spatial neglect (Schindler & Kerkhoff, 2004), may be more effective in manipulating spatial attention in HA, and in turn may influence the HLBE. Secondly, cues from another modality (acoustic, haptic) may prove more effective than cues delivered in the same – "impaired" - visual modality. Thirdly, spatial cueing may be very well effective in *acute* hemianopia, when the patients try to adapt to the sudden field loss (Machner et al, 2009), and develop compensatory strategies. This effect may have vanished after 9-12 months, when most of our patients were examined. This has to be tested in subsequent studies. Finally, *repetitive* spatial-attentional training instead of *transient* spatial cueing – such as recently employed elegantly in attention therapy for HA as a treatment for the visual search disorder (Lane et al, 2010) - may indeed reduce the HLBE transiently or even permanently. These are future issues that may help us to better understand the nature of the HLBE and the mechanisms of recovery from HA and associated visuospatial disorders. Finally, solving these issues may in the future lead to an effective treatment of the HLBE in HA which is at present not within reach.

Chapter III: General Discussion

This doctoral thesis studied the relationships between the HLBE, eccentric fixation, oculomotor search behavior, and spatial attention. The present three studies investigate by dint of the HLBE, as an appropriate neuropsychological operationalization of circumscribed spatial irritations after postchiasmatic brain damage, the contribution of these components for its emergence. All three studies showed that this contralesional error is a quintessential and exceedingly robust phenomenon in nearly all examined patients with homonymous visual field loss.

Since Axenfeld (1894) a whole slew of researchers has repeatedly approved this horizontal deviation (Barton et al., 1998; Doricchi, Onida & Guariglia, 2002, Hausmann et al., 2003; Kerkhoff & Schenk, 2011) also with other methods, such as the assessment of the visual subjective straight ahead (VSSA, Kuhn, Heywood & Kerkhoff, 2010). All authors conjointly documented disturbed spatial perceptions of the contralesional hemifield caused by unilateral brain lesions, primarily in hemianopic patients.

Bisection errors obviously are not just limited to the horizontal dimension, but also could be shown for the verticality in patients with altitudinal hemianopia (Kerkhoff, 1993).

Despite several hypotheses (Kerkhoff & Bucher, 2008) the mechanisms of emergence are still unclear. Oculomotor adaptation (Gassel & Williams, 1963) and eccentric fixation (Trautzettel-Klosinski, 1997) as well as increasing attention by spatial cueing as adjustment strategies, in order to broaden the visual search field, seemed to be promising approaches. Therefore their influence on the HLBE was analyzed in all three studies.

3.1 Summary

Obviously, the horizontal bias (HLBE) is not exclusively observable in cases of horizontal or vertical Heminanopia, but also in homonymous Quadrantopia (HQ), as shown in study I with 15 subjects with unilateral HQ. Interestingly only leftsided field defects deviated significantly from the objective midpoint, while rightsided HQ patient performed the linebisecting tasks quite accurately.

In contrast, irrespective of the affected quadrant, all HQ patients misjudged significantly their visual subjective straight ahead (VSSA). All patients deviated into their scotoma, in both the horizontal and the vertical orientation. Vertical shifts were larger in lower HQ than in upper HQ groups, while no such difference is to be noted for the horizontal shifts.

The biggest vertical shift was evidenced for the left lower HQ group, which correlates highly with subjectively circumscribed spatial uncertainties in judging visual depth when taking the stairs (Study I).

Statistical analyses of the intercorrelations indicated a high significance between the HLBE and the horizontal shift of the VSSA in HQ patients. Otherwise there were no significant correlations between vertical deviations of the VSSA and the HLBE.

It may be surmised that the oculomotor system aids in compensating the visual field loss by performing fast saccadic eye movements and fixations. Obviously, this degree of compensation (operationalized via the size of visual search field) and the HLBE were not significantly related to each other, thus rendering oculomotor or scanning deficits an unlikely explanation of the HLBE.

Mapping the blind spot revealed in none of all three studies a significant peculiarity, showing that static eccentric fixation was not present in the majority of patients studied. Morover, there was no significant correlation between the blind spot and the HLBE or the VSSA.

In Study II and III the starting position in the line bisecting tasks was systematically manipulated. The bisecting slit, moved by the experimenter according to the verbal commands of the participants towards the midpoint of the bar, started from 4 different positions: right end, left end (Study II, III) or mid-right and mid-left (Study III).

No significant correlations between the starting position and the HLBE were found, thus ruling out a spatial cueing effect on the HLBE with this paradigm.

Taken together, neither eccentric fixation nor spatial cueing could be detected in all three experiments as an assumingly active factor that favors the emergence of spatial-perceptive deviations, gaugeable by the HLBE and VSSA.

Nevertheless, all present studies demonstrated the existence of the HLBE which seems to be quite consistent and unswayable. In search of plausible reasons for this phenomenon, the applied measurement methods and other approaches should be discussed.

3.2 Eccentric fixation and blind spot mapping

The identification of a new retinal fixation locus is only reliably accomplishable with laser opthalmoscopes. As it is a question of a minimal displacement about 1-2°, it might remain undiscovered within perimetrical routine checkup (Trauzettel-Klosinski, 1997), especially because standard perimetry does not include eyetrack- and fundus-control.

Mapping the blind spot during perimetrical examination is an indirect way to exclude foveal shifts, without the complexity of a fundus-controlled assessment. Primarily, the blind spot mapping tests whether there is some deviation from the anatomically anticipated position of the blind spot in relation to the fovea. It also would allow conclusions about eccentric fixation during this testing. Obviously, eccentric fixation as measured by blind spot mapping can be ruled out in most of our patients with primarily *chronic* hemianopia. This may be different in acute cases. Moreover, *dynamic* fixational shifts during the performance of a bisection task can not be ruled out with the method of blind spot mapping.

Given that all participants had a time since lesion of at least 6 months (Study II: median for HA/right=11.5 months, HA/left=12.5 months, BD-controls=7.5 months; Study III: median for HA/right=13.0 months, HA/left=18.5 months, BD-controls=10.0 months) oculomotor adjustments subsequently from neurovisual rehabilitation and compensation in daily life can be assumed.

Taken together, the role of eccentric fixation for the emergence of the HLBE does not need to be definitely excluded yet. Rather, future studies should have another look at this issue, i.e. by studying dynamic fixation and oculomotor functions related to bisection.

3.3 Visuo-spatial distortions due to cortical "over-activation"

Another possibly helpful approach to the occurrence of the HLBE could be derived, analyzing other visual exploration techniques, required by linebisection tasks. To achieve the horizontal judgement patients have to scan permanently the blind hemifield with saccadic eyemovents, i. e. they use their fovea to find the "invisible" end of the line. The "visible" part of the line has not to be searched actively because it is allways "in sight" by the peripheral vision.

As a consequence neuronal responses in form of an over-activation of cortical neurons, which represent the central vision within the V1 region, have to be assumed, in sensu of a cortical magnification. This lateralized neuronal amplification could cause an asymmetrical activation in both occipital lobes with awkward effects on the spatial judgements (Reuter-Lorenz et al., 1990). This could possibly lead to a magnification of stimuli, perceived in the affected hemifield. To define the midpoint of a line, its complete length has to be measured and two equivalent sections have to be found, without underestimation or overestimation of one half. This would also explain why manipulation of the starting point did not influence the occurrence of the horizontal bias. No matter where the transector starts, in order to survey the whole length of the line, eyemovement has repeatedly to be brought into the blind hemifield.

Nielsen et al. showed in three experiments with faked hemianopia that all subjects biased consistently centripetally, which the authors explain as a shift towards the point of fixation (Nielsen, Intriligator & Barton, 1999). They assume modified perceptual conditions due to the constricted visualfield as the main reason for the upcoming horizontal deviation, postulating angle bisection instead of linebisection. This centralpetal displacement seems to be a normal phenomenon, provoked by stimulus exposure in only one visual hemifield. Apparently, if the line of sight ends into the objective midpoint of the stimulus, the performance becomes more accurate.

3.4 Mismatch-induced vestibular over-compensation

Given to the findings of reciproque visuo-vestibular inhibition mechanisms in the *intact* brain, the possibility of the HLBE resulting from vestibular overcompensation because of missing visual data (due to the field defect), in sensu of a visual deactivation (Brandt, 1998), should be discussed.

The visual field loss displays a persistent irritation in the interplay between the the PIVC and the visual cortices. To ensure spatial orientation, despite of the blind fields, affected patients have to deploy alternative strategies. Patients's awareness of their neurovisual deficit enforces higher attention and prudence, leading to emplified mental representation of the contralesional hemifield. From the clinical view, changes in self-monitoring and self-verbalization behavior are well reported by affected people. This would trigger a high concentration into the blind field, without visual-perceptive control but stronger analysis of only "imagined" spatial informations. Consequently, asked for line bisecting performance or other realistic spatial demands, the estimation of the missed vision range is magnified and causes spatial misjudgements into the blind hemifield.

This could be a scenario, explaining how the idea of reciproque visuo-vestibular inhibition according to Brandt et al. (2002) worked.

In consideration of the fact that about 10% of the optic nerve's axons wire up to the thalamic circuitry before running into the lateral geniculate nucleus (LGN) the question has to be asked which consequences this has. Theoretically, patients with lesions within the optic tract, i. e. pre-geniculate lesions, should show a minor manifestation of the HLBE than patients with postgeniculate lesions. This is in agreement with lesion studies of the HLBE (Zihl et al, 2009, Baier et al, 2010) who found a rather posterior occipital locus of those patients showing the typical HLBE. Moreover, this small portion of thalamic visual inputs reaches the parietal lobe via subcortical detours and may distract the occipito-parietal circuit (Kravitz et al., 2011) and facilitate dysfunctional relearnings of regulatory processes within the PIVC system.

3.5 Perspectives and clinical implications

In light of the above discussed ideas a stronger multisensory treatment of patients with neurovisual disorders and associated visuo-spatial disturbances, in particular the HLBE, seems recommended. This would imply, that simultaneously to conventional compensatory interventions, where saccadic eye movements into the blind field are extensively trained, the vestibular system could also to be "trained" or stimulated. This could for instance include galvanic-vestibular stimulation, a technique that can be easily and without side effects be administered (Utz et al., 2011).

Interestingly, such stimulation immediately modulates the ipsilesional line bisection error in patients suffering from left visuospatial neglect (Utz et al, 2011). Such modulatory techniques or other vestibular "trainings" (i.e. postural training) could aim towards a better self-awareness of possible overcompensating strategies, so that patients might learn to "switch" consciously between the visual or vestibular system to adjust to the visual loss. This might also help to reverse the tendency of many patients with visual loss to withdraw from life because they fear visual, motor or mental overload, andn because they try to avoid psychosocial embarrassement. Some patients with visual field deficits also complain about light symptoms of swaying vertigo provoked by the new experience of persistent visual insecurity and fast fatigue. Such multisensory treatments as mentioned above – which still have to be developed in detail – might also help to reduce anxiety and emotional disturbances in patients with homonymous visual field defects.

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