Disorders of Binocular Convergent Fusion and Stereoscopic Space Perception Following Acquired Brain Damage

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Treatment and Neuroanatomical Implications

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ABSTRACT

The unified and three-dimensional percept we perceive through the two of our eyes is the result of multiple interacting functional and neural processing stages in the visual brain. They range from convergence eye movements and sensory merging of the two disparate monocular images (binocular convergent fusion) up to an elaborated stereoscopic percept containing spatial depth (stereoscopic vision). Acquired disorders of binocular convergent fusion and stereoscopic vision of varying degrees are frequent sequels following damage to the brain, e.g. after a stroke or traumatic injury, among others. Typical symptoms of fusion impairment are blurred vision and/or diplopia after short periods of sustained binocular near space activities like reading or PC-work, usually accompanied by asthenopic symptoms like fatigue or eye pressure. Since fusion is a prerequisite of stereoscopic vision, difficulties in tasks that require precise judgements in visuo-spatial depth like grasping or taking staircases can occur. As a result, fusion impairment and associated deficits in stereoscopic vision can result in plain difficulties in almost all visual near-space activities of daily or vocational routines. The probably most severe deficit in stereoscopic vision can manifest in a complete failure to process or integrate any visual depth cues from the monocular images provided by our eyes resulting in a completely “flat” visual world (“flat vision”).

In the context of the constantly aging population alongside with an increased number of survivors from brain damage requiring re-integration in daily- and work-life, it appears unexpected, that no systematically evaluated treatment options have been available for these conditions so far. This circumstance surprises even more with regard to neurorehabilitation techniques in other visual domains, as there exist well-evaluated restitutional treatment strategies using perceptual (re-)learning paradigms grounding on repetitive systematic visual practice.
Consequently, the principal objective of this thesis was to evaluate in three consecutive studies the effectiveness of a novel binocular vision treatment designed for patients with acquired binocular convergent fusion and stereovision impairments of differential etiology:

Study 1 and Study 2 addressed the potential effects of this treatment in three different patient groups with impairments in convergent fusion and stereoscopic vision after cerebral hypoxia (Study 1), stroke and traumatic brain injury (Study 2). It was examined whether repetitive and

graded training of binocular convergent fusion with dichoptic devices could lead to improvements in binocular fusion and stereoscopic vision and to which extent the possible benefits might transfer to functionally relevant binocular tasks like reading. All patients were treated in a single-subject baseline design, with three baseline assessments before treatment to control for spontaneous recovery, followed by a treatment period of six weeks and two follow up assessments three and six months after the end of training. Repetitive dichoptic training was performed two times a week (one hour per session). After the treatment, the majority of patients in both studies improved significantly in binocular convergent fusion and stereoscopic vision. In addition, binocular reading time as an operationalization of binocular near-space activity of daily and vocational relevance significantly improved throughout the patients. The improvements in the variables of interest remained stable even after six months after training, indicating long-term stability of the achieved modifications. Importantly, no significant changes were observed during the baseline periods, thus ruling out spontaneous recovery as an explanation of the enhancement.

Study 3 states a case report describing unique patient EH who showed a complete loss of 3-D visual depth perception ("flat vision") together with an isolated impairment in binocular convergent fusion following right occipito-parietal hemorrhagic stroke. It was investigated whether perceptual re-training of binocular convergent fusion, almost identical to the one applied in Studies 1 & 2, would lead to a reinstatement of his spatial depth perception. Besides this functional perspective, a detailed lesion analysis was performed to get deeper insights on the neural contributions underlying this very rare condition of stereoscopic vision impairment. During three weeks of daily practice, a progressive and finally complete recovery in convergent fusion as well as subjective binocular depth perception was achieved. A voxel-based analysis of the patient's lesion revealed a selective damage to parieto-occipital area V6/V6A, which has been associated with the integration of multiple visual depth cues and convergence eye movements towards a refined 3-D percept in the recent past.

In sum, the results of the studies underlying the present thesis indicate a substantial treatment-induced plasticity of the lesioned brain in the perceptual re-learning of binocular convergent fusion and stereoscopic vision, thus suggesting the novel binocular vision treatment approach to be effective in principle. In addition, the findings provide new insights into the cortical

processing of visual 3-D space on both a functional and a neural level and give new hope and direction for the development of effective neurovisual rehabilitation strategies.

The published studies are attached in the Appendix of this dissertation.

Table of Contents

Index of Publications

Studies 1 and 2 depict the evaluation of a novel binocular vision training designed to treat patients suffering from acquired impairments of binocular convergent fusion and stereoscopic vision after cerebral hypoxia (Study 1), stroke and traumatic brain injury (Study 2). Study 3 investigates the functional and neuroanatomical correlates of complete binocular depth perception loss in consequence of a stroke as well as its modifiability by binocular vision training.

Study 1

Schaadt, A.-K., Schmidt, L., Kuhn, C., Summ, M., Adams, M., Garbacenkaite, R., Leonhardt, E., Reinhart, S., & Kerkhoff, G. (2014a). Perceptual re-learning of binocular fusion after hypoxic brain damage – four controlled single case treatment studies. *Neuropsychology, 28*, 382-387. DOI: 10.1037/neu0000019. IF[1] = 3.425.

Study 2

Schaadt, A.-K., Schmidt, L., Reinhart, S., Adams, M., Garbacenkaite, R., Leonhardt, E., Kuhn, C., & Kerkhoff, G. (2014b). Perceptual Relearning of Binocular Fusion and Stereoacuity After Brain Injury. *Neurorehabilitation and Neural Repair, 28*, 462-471. DOI: 1545968313516870. IF = 4.617.

Study 3

Schaadt, A.-K., Brandt, S.A., Kraft, A., Kerkhoff, G. (2015). Holmes and Horrax (1919) revisited: Impaired binocular fusion as a cause of "flat vision" after right parietal brain damage – A case study. *Neuropsychologia, 69*, 31-38. DOI:10.1016/j.neuropsychologia.2015.01.029. IF = 3.451.

[1] Impact factors (IF) according to Thompson Reuters for the year 2014.

List of Figures

Abbreviations

3-D: three-dimensional
TBI: traumatic brain injury

I. GENERAL INTRODUCTION

1. From the Eyes to a Cyclopean 3-D Percept: An Introduction to Binocular Vision

We see our world through two laterally placed eyes providing us two horizontally shifted, i.e. disparate images of a visual scene, which are continuously integrated into a single *cyclopean*[1] percept (see Figure 1). This integrational process is termed horizontal binocular fusion (Skelton & Kertesz, 1991). Compared to the composing monocular input, this *fused* binocular image has several advances: besides its prevention of diplopia during fixation, it provides a larger visual field, better visual acuity, and - probably most importantly - it plays a significant role in our perception of spatial depth (Cashell & Durran, 1989). Spatial depth perception based on binocular processing is defined as stereoscopic vision or stereopsis, respectively (Howard, 1995). Stereopsis significantly facilitates our vision as it helps us to localize the precise position of objects in three-dimensional (3-D) space and improves the accuracy of visually guided hand- and limb-movements, e.g. taking staircases or precise grasping. Moreover, from an evolutionary perspective, it has helped primates and carnivores to better track their prey and to properly react on obstacles during hunting or flight (Rizzo, 1989).

In addition to binocular depth cues derived from interocular disparity, our visual system also uses monocular input like differential monocular focusing and perspective, texture gradients, shading, image overlap or motion in the construction of a 3-D percept, but only the elaborated processing of binocular cues allows an *exact* perception spatial depth (Howard, 1995; Rizzo, 1989).

Binocular horizontal fusion and stereopsis are the results of multiple neurovisual processing stages involving a widespread anatomical and functional network of both serial and parallel information coding. They range from oculomotor responses as flexible eye-alignment when fixating objects at variable gaze positions to a rather cortical, i.e. sensory merging of the monocular inputs into one single stereoscopic percept (Skelton & Kertesz, 1991; Rizzo, 1989). As complex as this interplay appears to take place on a neural level, the extensive and variable are the symptoms that can result once a sudden disruption occurs, e.g. due to a stroke.

[1] The term cyclopean derives from cyclops, the one-eyed giants that based on their sole monocular perspective never experienced stereoscopic depth (Poggio & Poggio, 1984).

In the following, first an overview on the current perceptual and neural evidence inconvergent fusion and stereovision in the unlesioned visual system is given. Afterwards, their characteristics of impairment following acquired brain damage are described. Finally, this General Introduction ends with a synopsis on conceptual and neurobiological aspects of vision treatment alongside with the role of perceptual (re-)learning paradigms in neurovisual rehabilitation.

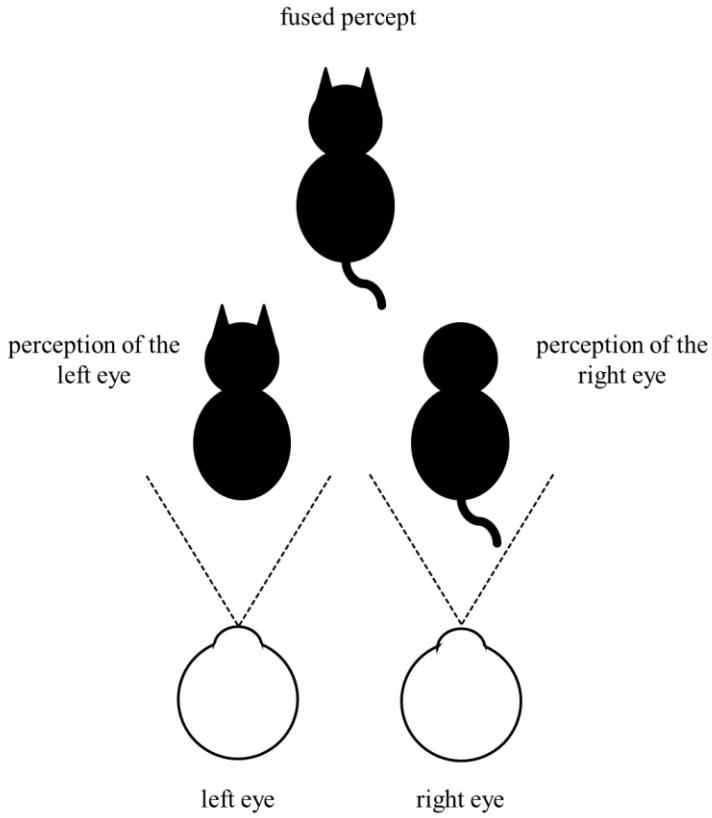

Figure 1. Schematic illustration of binocular convergent fusion.

1.1 Binocular Convergent Fusion

Binocular convergent fusion states the first step towards a cyclopean representation of our visual world. It can be subdivided into two subsequent stages: a motor component relying on flexible eye alignment (motor fusion) and a sensory component associated with the

neurovisual merging of the monocular images into a fused single image providing the perceptual basis for stereoscopic vision (sensory fusion; Skelton & Kertesz, 1991). The differential contributions of both components as well as their anatomical and functional background are subsequently described in detail.

1.1.1 Motor Fusion

The crucial stimulus for motor fusion is the disparity of the retinal inputs, i.e. when the monocular images are represented on non-corresponding retinal points. However, retinal correspondence is the essential cue for horizontal fusion. Consequently, to achieve correspondence of the bifoveal input while fixating a target, the eyes need to be adequately aligned (Rizzo, 1989). This is achieved by vergence eye-movements, which are characterized by the eyes moving in opposite (disconjugate) directions (Biousse & Newman, 2009). There exist two types of vergence – convergence and divergence. Bincoular convergence describes eye-alignment towards the nose (adduction), divergence describes oppositely directed eye-movements towards the horizontal visual periphery (abduction). Both types of disconjugate eye-movements are necessary for flexible switching of fixational targets in our surrounding visual space, but only sustained convergent eye-alignment resulting in intersectional monocular fields either achieved by adjacent convergence or divergence serves the processing of spatial depth information (Rizzo, 1989; Howard, 1995; Crone & Hardjowijoto, 1979).

Two antagonist extra-ocular muscles are involved in binocular horizontal vergence: the medial and the lateral rectus muscle (see Figure 2). Contraction of the medial and simultaneous stretching of the lateral rectus muscles leads to the adduction of the eyeball, i.e. initiation of binocular convergence. Conversely, stretching of the medial and contraction of the lateral rectus muscles leads to diverging eye-movement. On a neural level, the medial rectus muscle obtains its neural input by the oculomotor nerve (cranial nerve III; Biousse & Newman, 2009; Horn & Leigh, 2011). Its nucleus lies at the border of the periaqueductal gray matter atop the abducens nucleus in the brain stem (Horn & Leigh, 2011). On the other hand, the lateral rectus muscle is innervated by the abducens nerve (cranial nerve VI; Biousse & Newman, 2009), whose nucleus is located in the mesencephalic tegmentum pontis (Horn & Leigh, 2011). Besides the oculomotor nuclei of the cranial nerves III and VI, several other cortical and subcortical regions are involved in motor fusion, i.e. the frontal eye fields and lateral prefrontal areas, the visual cortices, lateral and medial parietal regions as well as

midbrain areas around the oculomotor nuclei and the cerebellum (Alkan, Biswal, & Alvarez, 2011; Van Horn, Waitzman, & Cullen, 2013; Kapoula, Yang, Coubard, Daunys, & Orssaud, 2005; Mays, 1984; Freeman & Ohzawa, 1990).

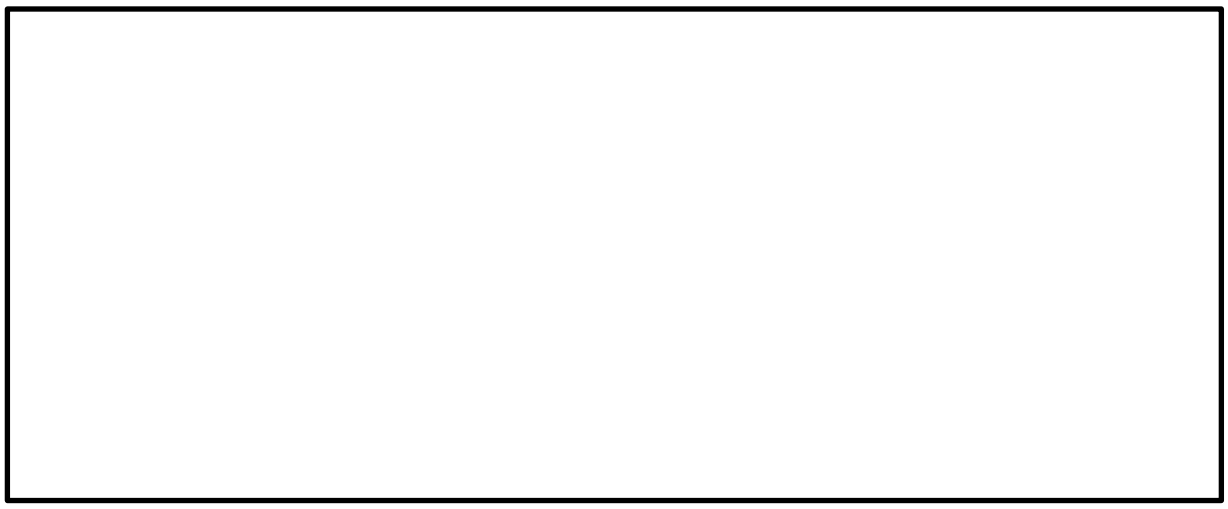

Figure 2[2]. Illustration of the action and location of the medial and lateral rectus eye muscle involved in convergent eye-movement. Modified from Brodal, P. (2004). *The central nervous system: structure and function* (p. 322). New York: Oxford University Press.

The differential interactions within and between these regions rely on a complex reciprocal feedback system between sensory visual afferences carrying information about the current visual perception and oculomotor efferences in order to sustain or change the point of fixation. For instance, receiving their input from the visual cortices in the occipital lobe and attentional processing units in prefrontal and parietal regions, the frontal eye-fields have been associated with the voluntary initiation and maintenance of convergence eye alignment (Alkan et al., 2011; Kapoula et al., 2005). The frontal eye-fields again project towards vergence-devoted cell areas in the midbrain, coding for gaze position and velocity of eye-movement (Zhang, Gamlin, & Mays, 1991; Mays, Zhang, Thorstad, & Gamlin, 1991; Mays & Gamlin, 1995; Van Horn et al., 2013). The cerebellum is most likely related to error detection and accuracy of vergence eye-movements, as supported by patient and primate studies

[2] Zur Wahrung der Lizenzrechte des Verlages wird diese Abbildung nicht dargestellt.

showing that cerebellar lesions and in particular of the cerebellar vermis lead to dysfunctional binocular convergence (Sander et al., 2009; Nitta, Akao, Kurkin, & Fukushima, 2008; see also Section 2).

Besides, the initiation of binocular vergence eye-alignment is accompanied by two monocular processes in order to provide a clear and "sharp" image of the currently focused stimulus: (1) the constriction of the pupil (miosis), and (2) accommodation, i.e. the dynamic refraction adjustment of the lens (fixation-accommodation-myosis synkinesis. AC/A, or near-response; Crone & Hardjowijoto, 1979; Ciuffreda, Rosenfield, & Chen, 1997; Richter, Lee, & Pardo, 2000).

1.1.2 Sensory Fusion

Whereas binocular convergence draws the first step towards a fused percept, the actual merging of the two disparate monocular images is perceived as a subsequently occurring neurocomputational process provided by fine-graded disparity coding. When the eyes are converged upon a fixated stimulus in the visual periphery, the monocular visual fields build an intersection of shared input in the frontal plane. Yet, not all stimuli within this corporate area are fused. As stated above, horizontal disparity is the essential prerequisite for the initiation of convergent eye movements, as only objects falling on corresponding retinal points can be fused (Rizzo, 1989). Within the intersectional visual field of binocular convergence, there exists a hypothetical curved line of points, where the images of each eye fall on corresponding retinal areas and are seen as single because of their zero disparity. This geometrical locus is named the horopter (Rizzo, 1989; Poggio & Poggio, 1984) and provides the optical basis for sensory fusion and further stereoscopic processing (see Figure 3). Besides the fused points lying directly on the horopter line, there exists a space before and behind where a small degree of retinal non-correspondence is tolerated by our visual system where fusion is still provided before diplopia occurs. This region of incomplete fusion before disparities are too large to be merged is defined as the Panum area (DeAngelis, 2000; Rizzo, 1989; Poggio & Poggio, 1984). Within the Panum area, two types of disparity can be differentiated, as illustrated by Figure 3. Objects located closer than the horopter formed by a given fixation point have a crossed disparity, as the visual axes intersect. The farer away from the horopter and the closer to the observer the fixational points are, the larger the disparity is between the comprising monocular images. Consequently, in order to bring those stimuli into visual fixation, a higher amount of convergence eye alignment is needed. On the other hand,

objects behind the horopter have uncrossed disparities and produce a relaxation of convergence, i.e. initiation of divergence eye-movements in order to achieve foveal focusing (Rizzo, 1989). In other words, viewing distance and the magnitude of disparity reflected in binocular convergence are highly interconnected and inverse proportional, respectively (DeAngelis, 2000). This relationship explains why disorders of binocular convergent fusion, which are described in Section 2, mainly manifest in the near space (Westheimer, 2009; Ptito, Lepore, & Guillemot, 1992; Poggio & Poggio, 1984; Julesz, 1986).

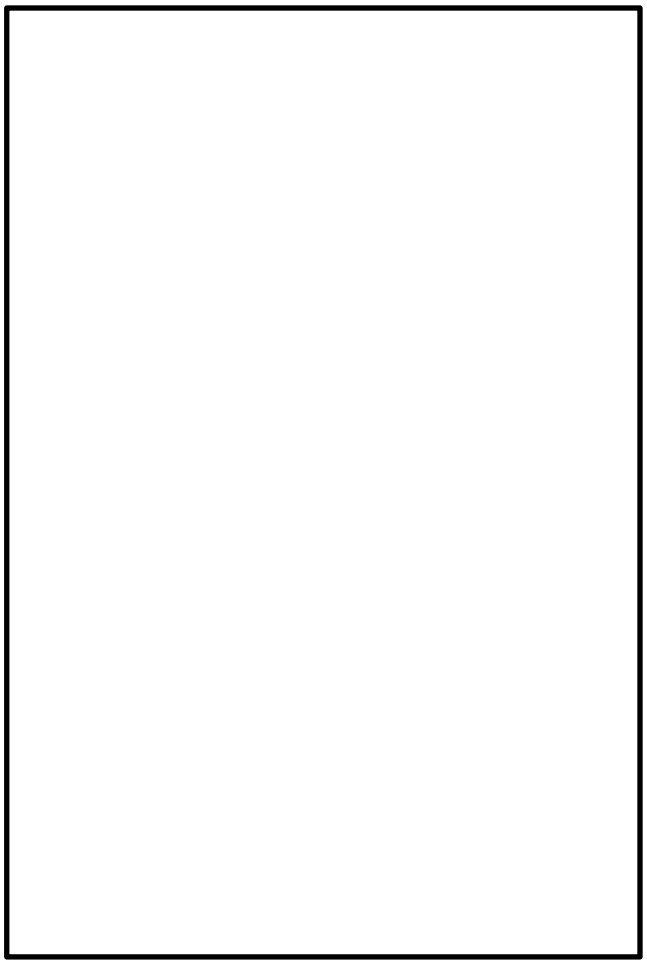

Figure 3[3]. Illustration of the horopter and crossed vs. uncrossed disparities. The horopter passes through the fixation point (F) as well as points L and M, which have zero disparity. Point U has uncrossed disparity, point C has crossed disparity. Modified from Wilcox, L.M.

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& Harris, J.M. (2010). Fundamentals of stereopsis. In D.A. Dartt (Ed.) *Encyclopedia of the Eye* (p.165). Oxford: Academic Press.

Contrary to the cortico-subcortical circuitry of convergence eye-alignment, sensory fusion relies on rather pure cortical neurovisual interactions. It however has to be noted, that sensory fusion and stereopsis are highly interconnected and a separation rather derives from a theoretical than a functional or neural perspective. Consequently, a clear distinction between the underlying brain regions devoted to sensory fusion versus stereopsis is difficult to draw (Westheimer, 2009).

Considering the visual processing pathway reaching from the eyes, the optic nerve and optic chiasm, the geniculate nucleus in the thalamus to the striate (primary) visual cortex (V1), the inputs of either eye remain functionally and physically segregated until V1, where the monocular input first converges (Rizzo, 1989; DeAngelis, 2000). Single cell recordings in monkeys have revealed highly specialized neurons in the primary and secondary (V2) visual cortex that fire for selective disparities on either side of the horopter by excitation versus inhabitation of firing the closer or the more far a given visual stimulus is away from the horopter (Poggio, Doty, & Talbot, 1977; Poggio & Talbot, 1981; Cumming & DeAngelis, 2001; Westheimer, 2009). Besides the striate cortex, disparity-selective though more coarsely tuned neurons were also found in higher order visual processing areas like V3 as well as in the parietal and temporal lobe (DeAngelis, 2000; Preston, Li, Kourtzi, & Welchman, 2008). Concerning the latter regions, they seem less important for the encoding but the elaboration of disparity signals towards the perception of stereoscopic depth, as described in the next section. With respect to sensory fusion, the neuroanatomical basis in terms of *pure* binocular merging appears to rely on rather low-level visual cortical processing anatomically supplied by early visual cortical areas like V1 and V2 (Van Essen & Gallant, 1994; DeAngelis, 2000; Orban, Janssen, & Vogels, 2006; Cumming & DeAngelis, 2001; Fortin, Ptito, Faubert, & Ptito, 2002; Ptito et al., 1992; Westheimer, 2009).

1.2 Stereoscopic Vision

As described in Section 1.1, sensory fusion represents an important cue for stereopsis as the disparity of the monocular images provides information about the exact spatial location of objects in the frontal plane. In concrete, the more the interocular images are separated within the Panum area, the bigger the depth perception of a stimulus relative to the fixation point of

the horopter appears once the monocular images are fused (DeAngelis, 2000). Thus, the greater the horizontal disparity between the monocular input, the higher the perceived depth. The cortical processing of stereopsis states a hierarchical process that inseparably connects to sensory fusion. Starting from V1, where fine-graded contour-based disparities like edges or dots are analyzed (local stereopsis), the processing stages move forward to extrastriate and higher-order visual processing areas of the parietal and temporal lobe in order to provide a more refined analysis of disparity information (global stereopsis; Rizzo, 1989; Bruce, Green, & Georgeson, 2003; Poggio & Poggio, 1984; Ptito et al., 1992; Westheimer, 2009; De Hamsher, 1978; Preston et al., 2008). In particular, brain regions devoted to global stereopsis have been revealed, inter alia, in the visual areae V2-V8 as well as in the medial superior temporal area (MST), the lateral occipital area (LO) and the inferior temporal area IT. Single-cell recordings have shown that these regions contain more coarsely tuned neurons that fire for distinct characteristics of disparity like e.g. magnitude or sign (De Hamsher, 1978; Ptito et al., 1992; Westheimer, 2009; DeAngelis, 2000; Preston et al., 2008; Poggio & Poggio, 1984).
From a rather holistic perspective, the cortical processing of stereopsis seems to follow the functional specialization of the visual system following the dorsal and ventral processing stream. Factually, visual areas V3, V5-V8, MST and LO are functionally and anatomically assigned to the dorsal pathway, that is devoted to the analysis of spatial relationships and object locations in visual space ("where"-pathway, see Figure 4) based on magnocellular

Figure 4[4]. Allocation and functional specialization of visual cortical areas (A) and their assignment to the dorsal ("where") and the ventral ("what") processing pathways (B).

[4] Zur Wahrung der Lizenzrechte des Verlages wird diese Abbildung nicht dargestellt.

Derived from Catani, M., & Thiebaut de Schotten, M. (2012). *Atlas of human brain connections* (pp. 303-304). New York: Oxford University Press.

projections from the retinae (Catani & Thiebaut de Schotten, 2012). On the other hand, areae V4 and IT belong to the ventral stream specialized on the detailed analysis of objects ("what"-pathway; Catani & Thiebaut de Schotten, 2012; see Figure 4), and are assumed to have different functions in disparity processing as compared to the dorsal stream, i.e. spatial figure-ground or scene segmentation and 3D-object recognition for example (Janssen, Vogels, & Orban, 1999; DeAngelis, 2000).

In sum, disparity-selective neurons exist in numerous visual cortical areas coding for differential aspects of stereoscopic processing. Though the selective properties in these regions seem to be well examined on a neurophysiological level, it is - until this date - however unclear, *how* and *where* exactly the visual brain integrates all this disparity information, conceivably together with monocular visual depth cues into a refined, integral 3–D percept which allows us to really see "the space between the objects" (DeAngelis, 2000). Probable neural "core" areas for this real 3-D computation appear higher order visual association cortices pending on magnocellular projections upon the dorsal stream. Experimental animal and human neuroimaging studies have shown several cortical regions in the parietal lobe to be connected with the integration of several visual depth cues leading to an integrated perception of visuo-spatial depth. For instance, Tsutsui et al. (2005) found neurons in the caudal intraparietal area (CIP) located in the caudolateral part of the intraparietal sulcus to be associated with the converging of both binocular and monocular cues (texture gradients) into a full stereoscopic percept. A second favorable brain region presumably devoted to cyclopean integration, is the area V6/V6A in the medial occipito-parietal cortex (Pitzalis et al., 2013). Contrary to CIP, V6/V6A relies more explicitly on pure binocular cues. As shown by human functional neuroimaging and single cell recording studies in animals, V6/V6A is perceived to be especially involved in the analysis of spatial locations of visual stimuli and the encoding of gaze positions in 3-D space by the integration of fixation distances and disparities (Galletti, Battaglini, & Fattori, 1995; Fattori, Pitzalis, & Galletti, 2009; Genovesio, Brunamonti, Giusti, & Ferraina, 2007). More concrete, V6/V6A contains so-called "sustained gaze-cells" selectively firing on different vergence positions, thus signaling the location in

space of fixated objects (Breveglieri et al., 2012). With respect to the differential hierarchical and parallel processing stages devoted to stereoscopic vision, this area might therefore play an important role towards connecting early binocular processing stages like motor and sensory fusion into a final cyclopean integration. The pivotal importance of V6/V6A concerning the computation of real 3-D perception is displayed in Study 3.

2. Disorders of Binocular Fusion and Visual 3-D Space Perception Following Acquired Brain Damage

As stated at the beginning, intact binocular capacities provide several advances as compared to monocular vision, e.g. increased visual acuity and contrast sensitivity due to binocular summation (Frisén & Lindblom, 1988), as well as a refined perception of spatial depth that allows us to accurately perform visual-motor tasks like grasping or walking staircases. Moreover, the fusional process prevents the perception of blur or diplopia (Rizzo, 1989; Howard, 1995). Since binocular fusion and stereopsis both rely on disparity processing, dysfunctions typically manifest in the near space because of the greater disparity of the monocular images in these distances. Once disturbed, these processes can have severe consequences on daily and vocational visual near space activities like reading, PC-work or navigation in visual space, only to name some of them. Moreover, with the advent of high-resolution displays on telecommunication devices like smartphones or tablet computers typically held within the arm-reaching distance, the requirements for binocular fusion have substantially increased during the last decades (Alkan et al., 2011).

With regard to the widespread network involved in binocular fusion and stereopsis ranging from the eyes to various cortical and subcortical areas, it is not surprising that disorders of either function or combined impairments are with a prevalence of approximately 40% (Danta, Hilton, & O'Boyle, 1978; Miller et al., 1999; Hart, 1969; Kerkhoff, 2000; Kraft et al., 2014) rather frequent sequels following acquired brain damage due to vascular disease or head trauma. Furthermore, they can occur in the context of inflammatory diseases like multiple sclerosis, neoplastic processes like tumors, neurodegenerative disorders (e.g. Parkinson's disease), or hypoxic brain damage, among others (Ciuffreda, 2002; Frohman, Frohman, Zee, McColl, & Galetta, 2005; Sobaci, Demirkaya, Gundogan, & Mutlu, 2009; Rizzo & Barton, 2008; Kerkhoff, 2000; Koh, Suh, Kim, & Kim, 2013). In addition, disorders of fusion and

stereopsis can further be due to congenital strabismus and amblyopia preventing an undisturbed development of binocular visual capacities (Rizzo, 1989).

Despite the high frequency and relevance of these disorders for daily and vocational visual routines, the research in this field has only been slowly growing in the nearer past. Especially with respect therapeutic options, there is a substantial lack of evaluated treatment strategies. Based on the oculomotor, perceptual and neural principles underlying binocular fusion and stereopsis provided by Section 1, the following paragraph seeks to give an overview about the symptoms, etiology and neuropathology, prevalence rates as well as the assessment and recovery concerning impairments of convergent fusion and stereoscopic vision following brain damage.

2.1 Convergent (Motor) Fusion Impairment

2.1.1 Symptoms

Convergent fusion impairment usually refers to a disturbance in the motor component of convergent fusion as sensory fusion and stereopsis are intersectional processes hardly to differentiate (see Section 1). Disorders of motor fusion typically manifest in blurred vision and horizontal diplopia, with vision blur being the preliminary stage of double vision. The symptoms are owed to the circumstance that the monocular images cannot be enduringly integrated into a single binocular percept after some time of binocular near space activity like reading, PC-work or smartphone handling. Instead, the perceived scenery of each eye horizontally drifts apart after usually less than 10-15 minutes of sustained binocular fixation periods (Stögerer & Kerkhoff, 1995; see Figure 5). The perceived emergence of blur and diplopia is often accompanied by an exodeviation of one or both eyes as the reciprocal system between motor and sensory fusion collapses. Inaccurate reading, a severely reduced reading duration and deficits in almost all types of binocular visual near space activity (e.g. object manipulation) due to the fuzzy or double sight are the typical consequences.

Besides, patients often experience asthenopic, i.e. eye-related complaints like eye-pressure, fatigue, headache, stingy or tired eyes, or tear hypersecretion respectively (Stögerer & Kerkhoff, 1995; Hart, 1969). As sufficient convergent eye-alignment is required for subsequent sensory fusional and stereoscopic processing stages, patients often show moderate to severe deficits in stereopsis since the disparity information cannot be sufficiently processed further when the eyes are not properly converged (Danta et al., 1978). Furthermore,

disturbances in motion perception especially under optic flow[5] conditions continuously requiring both fixation and adjustments in convergence angle can occur (Busettini, Masson, & Miles, 1997).

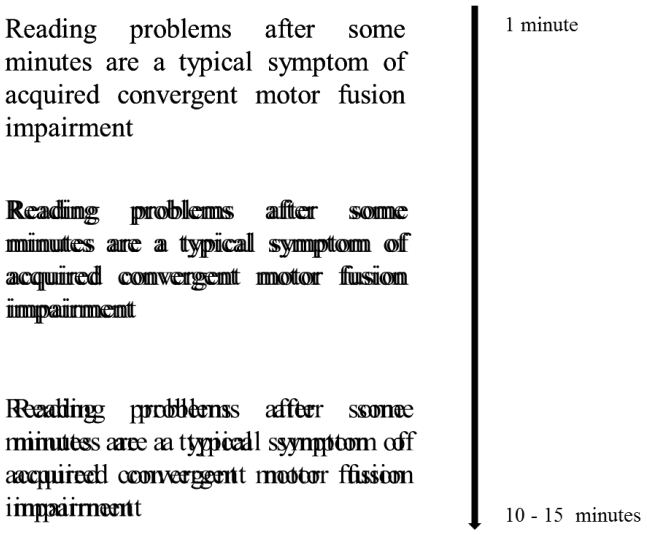

Figure 5. Illustration of emerging blur and diplopia in convergent motor fusion impairment after endured reading.

2.1.2 Etiology and Neuropathology

Disorders of convergent motor fusion are traditionally associated with brain stem lesions involving the oculomotor nuclei (Hart, 1969). Although lesion studies concerning fusion impairment following acquired brain damage are lacking, it is however likely that –with respect to the reciprocal cortico-subcortical network devoted to proper eye alignment and disparity coding described by Section 1 (Alkan et al., 2011; Kapoula et al., 2005; Sander et al., 2009; Preston et al., 2008), motor fusion impairment can also result from lesions in further areas devoted to disparity processing, e.g. the frontal eye fields, the cerebellum, or the primary and secondary visual cortices. For instance, Danta et al. (1978) found an inability to fuse dichoptic stimuli in two patients following focal occipital lesions. In addition, Patient EH

[5] Optic flow refers to the radial visual pattern that emerges during ego-motion in depth, e.g. when walking or riding on a bike (Lappe, Bremmer, & van den Berg, 1999).

of Study 3 showed a severe impairment in convergent motor fusion in the absence of subcortical lesion involvement.

2.1.3 Prevalence

With a prevalence of 20% after stroke and 30% after traumatic brain injury (TBI), disorders of convergent motor fusion are recurring sequels in the two big groups of acquired brain damage in neurorehabilitation centers (Barker-Collo, Wilde, & Feigin, 2009; Chard, 2006; Freeman, Hobart, Playford, Undy, & Thompson, 2005; Feigin, Barker-Collo, Krishnamurthi, Theadom, & Starkey, 2010). Furthermore, fusion impairment has been occasionally described after hypoxic brain damage, tumors, and inflammatory processes like encephalomyelitis disseminata or encephalitides, though concrete prevalence data are not available, yet (Ciuffreda, 2002; Frohman et al., 2005; Sobaci et al., 2009; Rizzo & Barton, 2008; Kerkhoff, 2000; Koh et al., 2013).

2.1.4 Assessment and Recovery

Convergent motor fusion is traditionally assessed as convergent fusional range by prisms (Cashell & Durran, 1989; Kaufmann & Steffen, 2012). Convergent fusional range describes the amplitude by which two horizontally presented disparate images separated by prisms in front of one eye can still be fused by the initiation of sustained convergence eye-alignment. The bigger the disparities between the monocular images due to increased prism amplitudes are, the larger is the convergence angle that has to be covered to maintain single vision (Cashell & Durran, 1989). Concerning normative data, there already exists a high variability in healthy subjects, which is probably due to asymptomatic micro-strabismus preventing maximum fusional capacities. Therefore, a clear line between normal and abnormal convergent fusion is hard to draw (Crone & Hardjowijoto, 1979). With respect to the patients examined and treated in Studies 1, 2 and 3, the majority however showed convergent fusional ranges below the lower cut-off derived from asymptomatic and healthy subjects. This indicates that the convergent fusional range is an appropriate operationalization of fusional capacities and matches well with the typical complaints described by the patient.

No recovery has been reported and no evaluated treatment strategies are available. This is surprising with respect to the high frequency of fusion impairment and the implications for the patient's (visual) activities of daily living. The need for evidence-based treatment

strategies gets even more obvious with respect to the very rare occurrence of spontaneous improvements of fusion impairment (McLean & Lee, 1998). For instance, Hart (1969) reported practically no recovery in five of seven patients within one year after traumatic brain injury.

2.2 Impairments of Stereoscopic Vision

2.2.1 Symptoms

Impairments in stereoscopic vision (astereopsis) can range from rather subtle deficits in stereoscopic processing up to a full loss of depth perception, manifesting itself in a completely flat visual world where every stimulus lies in the same frontal plane (Danta et al., 1978). The latter characteristic is highly unusual and has been only described in a few single case studies so far (Holmes & Horrax, 1919; Gloning, 1965; De Renzi, 1982; Michel, Jeannerod, & Devic, 1963). The first patient thoroughly examined that suffered from this condition was in a study from Holmes and Horrax (1919). They report a case with full depth perception loss following a gunshot wound that bilaterally affected the occipito-parietal cortices. As a consequence, the patient was completely unable to estimate any visual distances or object relations in depth (Holmes & Horrax, 1919). More fine-graded impairments of stereopsis are rather frequent conditions following acquired brain damage, resulting in more subtle impairments in the precision of visumotor tasks like grasping not necessarily noted by the patient (Sakata, Taira, Kusunoki, Murata, & Tanaka, 1997; Yoonessi & Baker, 2011; Danta et al., 1978).

2.2.2 Etiology and Neuropathology

The complete loss of binocular depth perception in terms of “flat vision” was only described in patients suffering from bilateral lesions affecting both the occipital and parietal cortices, whereas the patient in Study 3 showed a right-sided unilateral lesion. Concerning more fine-graded deficits, in global stereopsis, dominance of the right hemisphere and a less strict association towards occipital and parietal lesions seems to exist (Hamsher, 1978; Kraft et al., 2014). For instance, Danta et al. (1978) have described patients that show subtle impairments in global stereopsis presumably following right cortical regions that do not necessarily have to involve the striate cortex. Instead, global stereopsis depends significantly on the integrity of the temporal lobe, as revealed by studies with brain-damaged individuals (Ptito, Zatorre,

Larson, & Tosoni, 1991; Ptito & Zatorre, 1988). On the other hand, impairments in local stereopsis have not been connected to hemisphere-asymmetry and appear to rely more on occipital lesions involving the striate cortices (Ptito et al., 1992; Ptito & Zatorre, 1988; Ptito et al., 1991), as stated in Section 1.2. Moreover, local and global stereopsis impairments do not inevitably have to co-occur but can be separately present, supporting the presumed network of both hierarchical and parallel processing stages the neuroanatomical basis of stereopsis seems to rely on (Ptito et al., 1991). Furthermore, a frequent – though not strict – link between impaired stereopsis and homonymous field defects has been reported (Danta et al., 1978). This aspect together with the findings derived from the studies underlying this thesis will be addressed in the General Discussion.

2.2.3 Prevalence

Although the full loss of spatial depth perception has only been described in a few cases, more subtle impairments in stereopsis are frequent after brain damage. For instance, Danta et al. (1978) revealed a prevalence of 69% following right hemisphere stroke contrasting to 29% after left-sided brain lesions. In a more recent investigation by Kraft et al. (2014), half of the stroke patients assessed suffered from impaired stereopsis. Impaired stereoscopic processing also often occurs in the context of TBI (41%) as well as in other neurological conditions like multiple sclerosis (Sobaci et al., 2009) or Parkinson's disease (Koh et al., 2013). Furthermore, as motor fusion states an important cue for stereopsis, almost two thirds of patients suffering from fusion impairment show deficits in stereopsis, too (Stögerer & Kerkhoff, 1995).

2.2.4 Assessment and Recovery

Stereopsis is usually assessed as stereoacuity, defined as the visual ability to resolve finegraded binocular disparities. Stereoacuity tests are based on dichoptic stimuli that are presented to either eye. The lower the disparity between the images is, the smaller is the perceived stereoscopic depth once the images are binocularly integrated and hence the better is the stereoacuity. There exist two forms of stereotests differing in the type of stereopsis measures (local vs. global), the presence/absence of monocular cues and the mechanisms used to separate the visual images from the eyes (e.g. polarization or red-green glasses). Local stereopsis can be measured by tests containing contour-based monocular cues that however tend to overestimate the stereoscopic ability as the items can partially be already solved under

single eye conditions (Rizzo, 1989). A common test is the Titmus Test (Stereo Optical, Chicago), which was used as a measure of local stereopsis in Studies 1, 2 and 3. Global stereopsis is typically assessed using random dot stereograms that do not contain any monocular depth cues as the images presented to the eyes are not visible if they are not separated via special lenses. A common test for global stereopsis is the TNO Test (Lameris Ootech BV, Ede) which was used in Studies 2 and 3.

As with motor fusion impairment, there are no evaluated treatment strategies available for patients suffering from acquired brain damage. Indications that stereopsis can be re-acquired following brain damage in principle are supported by lesion studies in cats with bilateral striate areae ablations showing a full recovery of stereopsis after four doses of amphetamine (Feeney & Hovda, 1985). Besides, there exists some evidence on positive treatment effects on congenital astereopsis following repetitive training based on perceptual learning paradigms (Spiegel et al., 2013; Ding & Levi, 2011) as described in the next section.

3. Conceptual and Neurobiological Aspects of Binocular Vision Rehabilitation: The Role of Perceptual (Re-)learning

With respect to the rapidly growing population of elderly people alongside with an improved medical care at least in Western civilizations, the number of survivors of brain damage has extensively risen in the last years. Moreover, the higher survival rate does however also lead to an increased amount of subjects suffering from chronic disability that require long-term care and lifelong assistance. In the context of limited financial resources for healthcare, there is consequently a substantial need for effective treatment strategies (Chard, 2006; Freeman et al., 2005). Although the neuroanatomical bases of binocular fusion and stereoscopic vision, respectively have been extensively studied in the recent decades, potential treatment strategies have been nearly totally neglected ever since. This is surprising, as the impairments are frequent sequels following acquired brain damage and have a severe impact on the patients' functional independence, especially concerning the increased amount of near space activities in daily and work-life as described in the introduction. Moreover, there exist standard and evaluated diagnostic procedures for the assessment of both fusion and stereopsis since at least 40 years (Rizzo, 1989).

For the neurorehabilitation of other cerebral visual disturbances following acquired brain damage, there exist well evaluated compensatory and restorative treatment approaches (Kerkhoff, 2000; Kerkhoff, 1999; Kerkhoff, Munssinger, Haaf, Eberle-Strauss, & Stögerer, 1992; Funk et al., 2013). Concerning the latter, several studies using perceptual learning paradigms have revealed a substantial treatment-induced plasticity of the lesioned visual brain (Schoups, Vogels, & Orban, 1995; Huxlin et al., 2009). Perceptual learning refers to the enduring improvement in a specific visual task due to repetitive training (Ahissar & Hochstein, 2004; Gibson, 1953). For instance, studies on healthy participants have shown that the repeated practice in an orientation discrimination task of two lines with subsequently increased difficulty led to a significant improvement in the accuracy of their judgments (Vogels & Orban, 1985). In the binocular domain, the performance in stereoscopic tests was significantly enhanced after feedback-based training of the underlying material (Fendick & Westheimer, 1983). More recently, Spiegel and colleagues revealed that perceptual training of dichoptic visual stimuli in congenitally amblyopic adults led to lasting stereoacuity enhancements (Spiegel et al., 2013; Ding & Levi, 2011).

One important characteristic of perceptual learning is that the increased performance is highly specific with very limited transfer to related, though non-trained visual stimuli. On a neural level, this specificity indicates learning-induced modifications in “lower” visual processing levels, i.e. the primary visual cortices containing neurons that fire selectively on highly distinctive visual features (Fahle, 2005). Another characteristic of perceptual learning is the dependency of the task performance upon feedback, i.e. an improvement in the given task is particularly then achieved when the subject knows that the previously performed task was solved correctly vs. incorrectly (Fahle, 2005). This aspect leads to the hypothesis, that not only lower visual areas but also task-related “higher” visual areas associated with regulatory top-down mechanisms during learning are engaged in perceptual learning, via communicating in a reversed-hierarchy (Ahissar & Hochstein, 2004; Fahle, 2005).

As stated above, the positive effects of perceptual learning are not restricted to healthy individuals. For example, Funk et al. (2013) showed that the performance of stroke patients with visual perceptive deficits in a line orientation discrimination task could be significantly improved after systematic feedback-based training. Moreover, the treatment effects partially generalized upon related visuospatial tasks, e.g. writing and visual-constructive abilities. Importantly, the results were stable in a two month follow up investigation indicating a

training-induced long-term modification of the lesioned visual system (Funk et al., 2013). These results are encouraging as they suggest that neuroplasticity in the visual domain is possible in principle. Whether and to which extent perceptual (re-)learning can be achieved in the context of impaired binocular fusion following differential etiologies of acquired brain damage was the aim of the Studies 1, 2, and 3.

II. GENERAL DISCUSSION

1. Rationale of the Underlying Investigations

Regarding the substantial lack of evaluated treatment strategies in the face of the profound functional consequences for daily and vocational routines arising for patients with acquired impairments of convergent fusion and stereovision, the major objectives of this thesis were to assess the effectiveness of a novel binocular treatment approach based on repetitive dichoptic practice according to the principles of perceptual learning (Study 1, Study 2). In addition, the neural and functional contributions as well as their potential modifiability with this novel treatment were investigated in a patient suffering from of complete depth perception loss ("flat vision") after a right-sided stroke (Study 3; see Figure 6):

Study 1 and *Study 2* examined the effects of this treatment in three different patient groups with convergent fusion impairment and astereopsis resulting from three different etiologies, i.e. cerebral hypoxia (Study 1), stroke and traumatic brain injury (Study 2). It was investigated, whether repetitive and graded training of binocular convergent fusion with dichoptic devices would lead to an improvement in convergent fusional range and stereoacuity and to which extent this potential improvement would transfer to related binocular tasks like reading duration. Furthermore, Study 2 considered potentially differential treatment effects based on the etiology of brain lesion, as stroke and traumatic brain injury differ substantially in their neuropathological mechanisms of brain damage.

Study 3 describes a unique patient showing a full loss of 3-D visual depth perception ("flat vision") after a right occipito-parietal hemorrhage, almost identically to the first case study provided by Holmes and Horrax (1919). All objects in is surrounding visual world appeared equidistant to him, thus experiencing an entire deficit in the processing of visual depth cues ("flat vision"). Besides his "flat vision", he only showed deficits in convergent fusion as well as bilateral lower visual field loss. It was assessed to which extent the treatment of convergent fusion using a comparable training design as in Studies 1 & 2 could lead to a reinstatement of his spatial depth perception. Moreover, a detailed lesion analysis was performed in order to get new insights concerning the ongoing debate on a pivotal "core" area devoted to the neural integration of the different depth cues into a full 3-D percept.

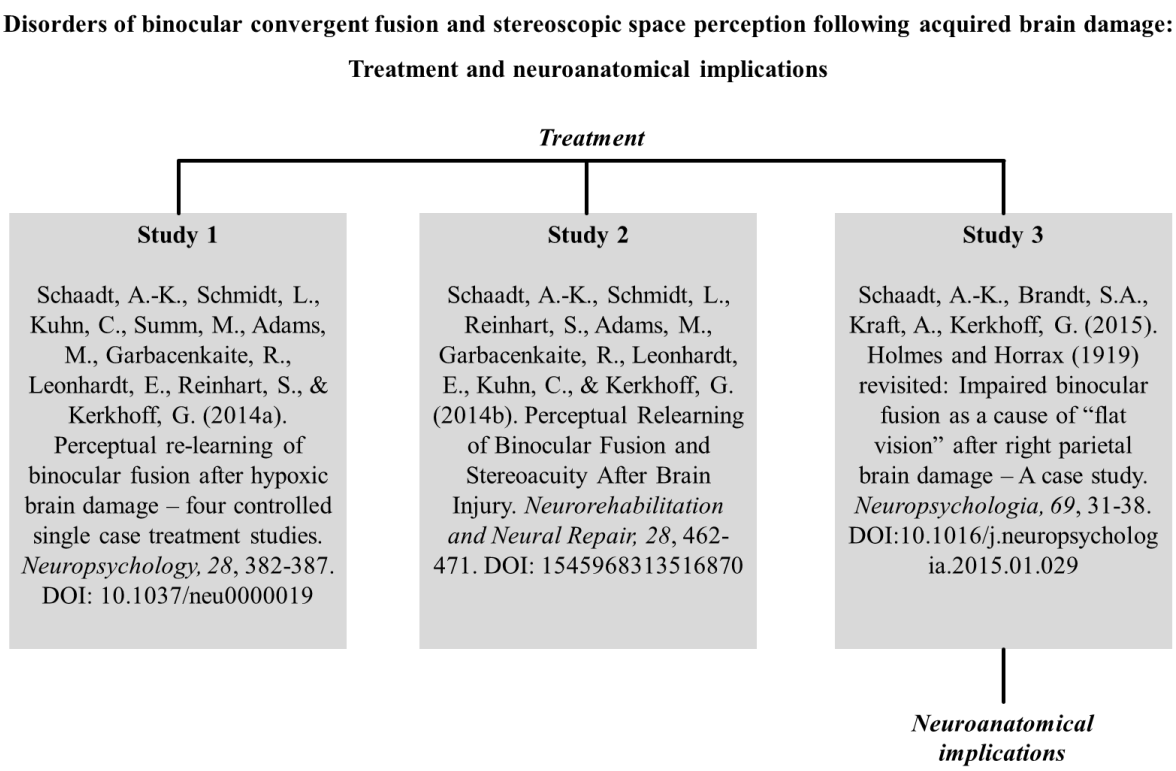

Figure 6. Graphic delineation of the studies underlying the present thesis.

In the following, first a summary of the major results is given before they will be discussed in the light of the current literature concerning their implications on the neuroplasticity of the lesioned binocular system, the usability for neurorehabilitation and the neural computation of 3-D space vision. At the end, perspectives for future research as well as a general conclusion are provided.

2. Summary of the Major Results

Study 1: Perceptual Relearning of Binocular Fusion After Hypoxic Brain Damage: Four Controlled Single-Case Treatment Studies

In a single-subject baseline design, four patients suffering from with severely reduced convergent fusion and stereopsis after hypoxic brain damage were treated. Three baseline assessments before treatment were performed to control for spontaneous recovery, followed by a treatment period of six weeks and two follow up assessments three and six months after the end of training. Repetitive dichoptic training was performed two times a week (one hour per session) with three different devices (prisms of increasing diopters, dichoptic stimuli,

cheiroscope) in order to slowly increase convergent fusion by ascending disparity angles. After the treatment, all 4 patients improved significantly in binocular fusion and 2 of 4 patients improved significantly in local stereopsis. Furthermore, subjective reading time until the emergence of diplopia, taken as a measure of the functional implications of fusion impairment, increased significantly in all patients throughout the training. Importantly, no significant changes were observed during the baseline and follow-up periods. Furthermore, no significant improvements were revealed in the additionally assessed visual control variables, i.e. near and far visual acuity as well as monocular accommodation.

Study 2: *Perceptual Relearning of Binocular Fusion and Stereoacuity After Brain Injury*

The same treatment design as in Study 1 was applied to 11 patients with stroke and 9 patients with TBI. After treatment, both groups showed considerable and lasting improvements in convergent fusion, local and global stereopsis, binocular reading duration as well as slightly increased near visual acuity. Far visual acuity and accommodation remained unchanged. Again, no changes in the assessed variables were observed during treatment-free periods at baselines and follow-up measurements. Despite the overall positive treatment effects, the stroke group showed a higher training benefit on convergent fusional range, whereas the opposite pattern was observed in binocular reading duration.

Study 3: *Holmes and Horrax (1919) Revisited: Impaired Binocular Fusion as a Cause of "Flat Vision" After Right Parietal Brain Damage – A Case Study*

A unique patient (EH) suffering from a total loss of visual depth perception after a large right-sided occipito-parietal hemorrhage is described. Neurovisual assessments revealed field loss in both the lower visual quadrants accompanied by a severely impaired binocular convergent fusion, but preserved local and global stereopsis. Perceptual re-training of binocular fusion in a slightly modified manner as compared to Studies 1 and 2 but using the same treatment devices led to a progressive and finally complete recovery in convergent fusion as well as subjective binocular depth perception. Interestingly, the latter recovered gradually from far- to near-space. This indicates an interaction of binocular convergent fusion and its recovery during therapy with observer distance. In addition, objective visual depth estimation of relative distances in the frontal plane improved, whereas stereopsis was only slightly impaired and did not change during treatment. A detailed voxel-based lesion analysis revealed a selective involvement of area V6/V6A, which has been in current literature stated to be significantly involved in the integration of multiple depth cues into a real visual 3-D percept.

3. Neuroplasticity in the Lesioned Binocular Brain

3.1 Implications of Perceptual (Re-)Learning

In all studies, the treatment applied led to a substantial increase of binocular capacities, indicating a considerable plasticity of the lesioned brain. Importantly, this plasticity was independent from the chronicity of lesion (see Study 2), but - with one exception (near visual acuity in Study 2) - restricted to binocular variables, namely convergent fusion, stereopsis of varying degree and reading duration. This fact bares two main implications: neuroplasticity is possible in principle in the lesioned binocular system (1), but highly specific to the binocularity of tasks (2). Concerning the first fact, the current results are in line with the broad evidence on neuroplasticity, stating that learning is not restricted to the juvenile healthy but as well possible in the adult and moreover in the lesioned brain (see Kaas, 1991; Kleim & Jones, 2008, for review). With respect to the specificity of the re-acquirement, the current findings replicate the results of visual treatment effects in other visual domains, e.g. visuospatial processing. For instance, when comparing the current results with the study on line orientation discrimination training of Funk and colleagues (Funk et al., 2013), our results yield largely the same pattern: Domains that are rather directly associated to the trained function profit from specific treatment, whereas transfer effects diminish the less associated the visual functions are. This limited transfer characteristics revealed through repetitive practice are congruent to the paradigms of perceptual learning the design of the studies grounded on, portending that transfer within the same domain as the trained task can occur but gets less likely the more unrelated the visual tasks are (Fahle, 2005).

The positive effects of repetitive practice raise the question how perceptual relearning of binocular visual functions is represented on a neural level. Perceptual learning is assumed to rely on mechanisms that involve both bottom-up and top-down processes for task improvement (Fahle, 2005). Binocular fusion on the other hand is perceived to be neurally supplied by a widespread cortico-subcortical network involving the striate and extrastriate cortices, frontal eye-fields and the brainstem, among others (Alkan et al., 2011; Van Essen & Gallant, 1994; DeAngelis, 2000; Orban, Janssen, & Vogels, 2006; Cumming & DeAngelis, 2001; Fortin et al., 2002; Ptito et al., 1992). Damage to some area leading to fusion impairment might be compensated by a treatment-induced recruiting of healthy cortex regions also involved in disparity processing. This could be provided by higher-order visual areas devoted to disparity coding, what would be in line with the reverse hierarchy perceptual relearning is assumed to partially ground on (Ahissar & Hochstein, 2004). Put differently,

top-down processing mechanisms might facilitate modified disparity coding in lower visual areas, e.g. the striate cortices. By modification of disparity coding in these areas, they (bottom up) provide sufficient information again for further binocular analysis, i.e. stereopsis or 3-D vision itself.

3.2 Constraints of Improvements

Although the treatment revealed promising and lasting effects, not all patients equivalently benefitted from the treatment. More concrete, Study 2 revealed a significantly lower training benefit concerning convergent fusion in the patients suffering from traumatic brain injury as compared to the stroke patients. Interestingly, this pattern was not evident in local stereopsis but inverse concerning binocular reading duration. Furthermore, in both Studies 1 and 2 there were non-responders to the training. This individual variability within the though promising group effects suggests several constraints on the neuroplasticity derived from perceptual re-learning.

Concerning the differential treatment effects in binocular fusion depending on the etiology of brain damage, the lower improvement in the TBI group can be explained by the characteristics and neuropathology of brain damage caused by stroke vs. TBI. In contrast to stroke that majorly leads to focal, circumscribed lesions rather involving cortical structures, traumatic injury to the brain is characterized by widespread and large both cortical as well as subcortical lesions often affecting the brainstem and deriving pathways due to diffuse axonal injuries (Feigin et al., 2010; Rosenblum, Greenberg, Seelig, & Becker, 1981; Firsching, Woischneck, Klein, Ludwig, & Döhring, 2002). With regard to the plenty of brain regions involved in binocular fusion it is likely that traumatic brain injury has affected much more convergent-fusion-related areas than a rather focal stroke, thus limiting the capacities of the binocular brain to adopt for damaged units following repeated practice. Furthermore, as comorbid brain stem lesions are much more common after TBI (Firsching et al., 2002), the putative involvement of the oculomotor nuclei in the brainstem essential to convergence initiation, i.e. motor fusion might further explain the lesser extent of fusion improvement in the TBI group. The size and site of brain lesion possibly affecting critical regions devoted to disparity processing might also explain the course of non-response to the training in a patient of the stroke group (Nr. 8; Study 2), whereas the concrete characteristics remain speculative as no lesion data were available for proofing this hypothesis.

Concerning stereopsis within Study 2, interestingly no etiology group effects were evident. Furthermore, in all patient groups there was a restricted number of single patients, including EH of Study 3 that improved in fusion but not in stereopsis or vice versa. These findings indicate that convergent fusion might be a necessary though not sufficient cue towards stereopsis. In other words, fusion facilitates stereopsis but it is not the single determining factor, indicating a only partial correlation. This view is supported by the results of Study 3 showing that changes in fusion and full 3-D vision can occur independently of stereoacuity performance.

With respect to reading duration in Study 2, the opposite pattern as compared to the results in convergent fusion was shown. Here, the stroke patients had a lower gain than the TBI patients. In contrast to the explanation of group differences in convergent fusion, varying lesion characteristics are unlikely to hold for the better outcome in the TBI group. Rather, the differences in reading duration can be better explained by an age-bias between the two groups as the stroke group was significantly older than the TBI group. Aging is typically accompanied by a variety of neural and non-neural changes, like decreases in eye-function through thickening of the lens (Barker-Collo, Wilde, & Feigin, 2009), that might be responsible for the lesser training benefit in this visual task.

4. Neuroanatomical Considerations on 3-D Space Perception

As stated in Chapter I, binocular fusion and stereopsis seem closely connected both on a functional and neural level by representing different steps within a certain hierarchy of disparity coding. With exception to the few differential responders discussed in the section above, Studies 1 and 2 replicated this close correspondence on a group level. The results of Study 3 however challenge this connection, as EH showed a severe fusion impairment comorbid to his “flat vision” despite almost normal local and global stereopsis. Moreover, the treatment led to a significant improvement in convergent fusion accompanied by a graded reinstatement of real 3-D depth perception while stereopsis remained unaffected. This observation indicates that complete depth perception loss can result from an isolated impairment in convergent fusion. As introduced in Chapter I, several areas within the posterior parietal lobe have been in the nearer past associated with the integration of the multiplicity of depth cues derived from magnocellular projections towards a refined stereoscopic percept, i.e. CIP and V6/V6A (Tsutsui et al., 2005; Pitzalis et al., 2013; Fattori et

al., 2009; Galletti et al., 1995; Genovesio & Ferraina, 2004). A detailed delineation and analysis of EH's brain lesion showed that the right area V6/V6A has been destroyed by his hemorrhage. V6/V6A is assumed to play an important role in the integration of sustained convergence eye-alignment and the coding of object locations in depth (Galletti et al., 1995; Genovesio & Ferraina, 2004; Breveglieri et al., 2012). The involvement of this area together with the symptoms displayed by the patient – namely fusion impairment and "flat vision" – encourage the hypothesis towards a causal link between fusion and 3-D perception that does not necessarily has to involve distinct features of stereoscopic processing as assessed by local and global stereotests. This view is supported when a closer look on the few previously reported cases suffering from complete depth perception loss is provided, as the majority of patients has shown oculomotor disturbance leading to severe forms of fusion impairment, e.g. by squint or convergence insufficiency (Michel et al., 1963; Gloning, 1965).

Moreover, from a more global point of view, the affection of only the right-sided area V6/V6A in EH's case is in line with current evidence highlighting the importance of the right hemisphere in (binocular) visuospatial processing (Rizzo, 1989; Danta et al., 1978; Kerkhoff, 2000; Kraft et al., 2014).

4.1 Role of Visual Field Defects

A further appealing parallel when comparing EH to the previously published cases on "flat vision" is the bilateral inferior field loss. On a functional level, the lower visual field is highly relevant in everyday life concerning the perception and use of visual depth information. For instance, when we walk on uneven ground or on staircases, we see those stimuli below the horizontal line artificially dividing the lower from the upper quadrants. This is also the case when we manipulate or reach for objects in depth, as our arms and hands are located below our eyes. The putative involvement of lower visual field loss in "flat vision" raises the question whether this is a frequently associated phenomenon due to lesion proximity or if it serves as a necessary requirement of "flat vision" or fusion impairment itself. Interestingly, regarding the patient characteristics of Studies 1 and 2, 13 out of 24 patients showed visual field defects, too. However, they were of varying severity and quadrant involvement, and – most importantly- with no experience of "flat vision". This rather frequent co-occurency of visual field defects and convergent fusion impairment is appealing, replicating the findings of Danta et al. (1978) as well as ablation studies in cats with respect to stereopsis. The connection might on the one hand result from shared or neighbored brain (lesion) areas, as the striate and extrastriate visual cortices are both involved in visual field representation (Catani

& Thiebaut de Schotten, 2012) and binocular merging on a sensory level (Westheimer, 2009; Preston et al., 2008; Rizzo, 1989; DeAngelis, 2000). On the other hand it is possible that field loss might cause a stereo-correspondence problem as one of the disparate monocular images might fall into the scotoma. However, visual field loss per se is not sufficient for the emergence of "flat vision". Instead, at least an affection of bilateral lower quadrant loss together with fusion impairment seems required. Whether this explanation holds true and whether there is indeed a causal link between visual field loss, fusion impairment and/or "flat vision" as has to be clarified in future studies.

5. Implications for Neurorehabilitation

As stated in Chapter I, acquired dysfunctions of convergent fusion and stereovision are recurring sequels following acquired brain damage. Despite their high frequency, they have been almost completely neglected in visual neurorehabilitation so far and no evidence-based treatment has been available, yet. This is dramatic as both fusion impairment and stereoscopic vision have a severe impact on the patients' functional independence: Since they typically manifest in the visual near space, they have substantial consequences on important binocular activities like reading or PC-work due to emerging blur and diplopia or accurate visual-motor tasks like grasping and object manipulation. Especially with respect to work-life, the demand of endured binocular activities within fixed near distances in reading, PC-Work or smartphone use has risen in the last decades, indicating a need for effective treatment. Moreover, regarding the constantly aging population and delayed onset of retirement alongside with improved medical care leading to a higher amount of survivors of brain damage (Chard, 2006; Freeman et al., 2005), the necessity of successful binocular vision rehabilitation gets even more obvious.

In all three studies, the repetitive dichoptic training led to substantial and lasting improvements in convergent fusion, stereoscopic perception as well as binocular visual activites of daily living, thus covering the main demand towards neurovisual rehabilitation strategies, i.e. effectivity. This effectivity is also displayed in the promising effect sizes of the improvement in the binocular variables of Studies 1 & 2. Moreover, in the context of limited financial resources provided to healthcare systems, successful neurorehabilitation techniques do not only need to be effective per se, but also highly economic. In the present investigation, the positive effects of the training where achieved within less than 30 hours of practice on average within circumscribed period of six to eight (Studies 1 & 2) and three weeks (Study 3).

This indicates rather low costs, bearing in mind that all improvements remained highly stable without any further treatment in follow- up assessments several months post-training. Despite the studies of this thesis served as proof-of-principle and their results have to be replicated and extended in further investigations (see Section 6), the novel binocular vision training used here seems to be an ideal restitutional treatment approach suitable for visual neurorehabilitation.

6. Perspectives

Despite their above discussed promising results and implications for neurorehabilitation, the three studies underlying the present thesis give rise for further research questions and perspectives. For instance, concerning the use of perceptual (re-)learning paradigms in neurorehabilitation, Studies 1-3 depict an extension of the current evidence in reference to binocular capacities (Funk et al., 2013). How perceptual re-learning of convergent fusion and stereopsis or real 3-D vision, respectively however actually occurs in the brain remains obscure, especially with respect to the question where the binocular brain compensates for the functional loss. This issue could be investigated by the use of functional neuroimaging techniques applied before and after treatment, an approach that is currently extensively studied in motor neurorehabilitation (see e.g. Cauraugh & Summers, 2005, for review). Assigned to the visual domain, such examinations could reveal potential changes in the activation of the putative brain areas devoted to fusion, stereopsis and integrated spatial depth perception.

The use of imaging techniques might as well be of interest regarding the potential non- and differential responders to the treatment as seen in Studies 1 and 2. Here, a detailed lesion analysis as performed in Study 3 could bring important insights on brain regions that potentially have to be necessarily preserved to obtain improvements by binocular vision treatment. Moreover, lesion investigations might be helpful concerning the presumably more cortical lesions underlying convergent fusion impairment (Danta et al., 1978). This is especially of interest with regard to the striate cortices due to the probably close, though not strict association of visual field defects with fusion impairment and deficits in spatial depth perception (Danta et al., 1978; see Chapter I). Concerning the latter, Study 3 has revealed that a complete loss of spatial depth perception in terms of "flat vision" can occur and be modified in the absence of severe deficits or treatment-induced changes in stereopsis. This is surprising, as stereopsis is traditionally counted a necessary cue for the synthesis of a cyclopean percept

(Rizzo, 1989). Though the condition of "flat vision" is a very rare one, examinations of future cases should bear this contradiction in mind.

With regard to Studies 1 and 2, the evaluation of the dichoptic training addressed three important etiology groups, i.e. stroke, TBI and cerebral hypoxia. As stated in Chapter I, disorders of convergent fusion and stereoscopic vision can however occur in way more etiologies of acquired brain damage. As differential training benefits were observed between patients suffering from stroke versus TBI (Study 2), an extension of the binocular vision treatment towards other courses of brain damage, e.g. multiple sclerosis would be interesting.

Finally, Studies 1, 2 and 3 only served as proof-of-principle studies to assess the potential success of the treatment method. Even though improvements in the assessed binocular variables could be significantly obtained and did not occur during treatment-free periods, an evaluation of the training using a control group design, e.g. in terms of waiting control patients with randomized assignment to the two different groups would be preferable for subsequent studies.

7. General Conclusion

The three studies comprising the present thesis provided a successful evaluation of a novel binocular vision treatment based on the principles of perceptual (re-)learning that led to substantial and lasting improvements in convergent motor fusion and stereopsis as well as visual depth perception. On the other hand, they yield new insights towards an improved understanding of visual 3-D space processing on both a functional and a neural level. To conclude, the sum of results indicates a substantial treatment-induced plasticity of the lesioned visual brain in the perceptual re-learning of binocular and visuospatial capacities. Moreover, it provides new hope and direction for the development of further effective neurorehabilitation strategies to treat deficits in binocular fusion and stereoscopic vision but also other neurovisual disorders resulting from acquired brain damage.

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Complete Publication List

Peer-reviewed Journal Articles

In press

Neumann, G**, Schaadt, A.-K**., Reinhart, S., & Kerkhoff, G. (in press). Clinical and psychometric evaluations of the Cerebral Vision Screening Questionnaire in 461 non-aphasic individuals post-stroke. *Neurorehabilitation & Neural Repair.* IF = 4.617.

Oppenländer, K., Utz, K. S., Reinhart, S., Keller, I., Kerkhoff, G., & **Schaadt, A.-K**. (2015). Subliminal galvanic-vestibular stimulation recalibrates the distorted visual and tactile subjective vertical in right-sided stroke. *Neuropsychologia*. DOI:10.1016/j. neuropsychologia.2015. 03.004. IF = 3.451.

2015

[6] **Schaadt, A.-K., Brandt, S.A., Kraft, A., Kerkhoff, G. (2015). Holmes and Horrax (1919) revisited: Impaired binocular fusion as a cause of "flat vision" after right parietal brain damage – A case study. *Neuropsychologia, 69*, 31-38. DOI:10.1016/j.neuropsychologia. 2015.01.029. IF = 3.451.

2014

** **Schaadt, A.-K**., Schmidt, L., Kuhn, C., Summ, M., Adams, M., Garbacenkaite, R., Leonhardt, E.,Reinhart, S., & Kerkhoff, G. (2014a). Perceptual re-learning of binocular fusion after hypoxic brain damage – four controlled single case treatment studies. *Neuropsychology, 28* (3), 382-387. DOI: 10.1037/neu0000019. IF = 3.425.

[6] Dissertation-relevant publications are marked with asterisks.

** **Schaadt, A.- K**., Schmidt, L., Reinhart, S., Adams, M., Garbacenkaite, R., Leonhardt, E., Kuhn, C., & Kerkhoff, G. (2014b). Perceptual Relearning of Binocular Fusion and Stereoacuity After Brain Injury. *Neurorehabilitation & Neural Repair, 28*(5), 462-471. DOI: 1545968313516870. IF = 4.617.

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Book Chapters and Monographs

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Schaadt, A.-K. & Kerkhoff, G. (in press). Vision and visual processing disorders. In: M. Husain, & J. Schott (Eds.) *Oxford Handbook of Cognitive Neurology & Dementia*.

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Appendix: Original Research Articles

Appendix A:

Schaadt, A.-K., Schmidt, L., Kuhn, C., Summ, M., Adams, M., Garbacenkaite, R., Leonhardt, E.,Reinhart, S., & Kerkhoff, G. (2014a). Perceptual re-learning of binocular fusion after hypoxic brain damage – four controlled single case treatment studies. *Neuropsychology, 28* (3), 382-387.

Appendix B:

Schaadt, A.- K., Schmidt, L., Reinhart, S., Adams, M., Garbacenkaite, R., Leonhardt, E., Kuhn, C., & Kerkhoff, G. (2014b). Perceptual Relearning of Binocular Fusion and Stereoacuity After Brain Injury. *Neurorehabilitation & Neural Repair, 28*(5), 462-471.

Appendix C:

Schaadt, A.-K., Brandt, S.A., Kraft, A., Kerkhoff, G. (2015). Holmes and Horrax (1919) revisited: Impaired binocular fusion as a cause of "flat vision" after right parietal brain damage – A case study. *Neuropsychologia, 69*, 31-38.

Appendix A[1]:

Schaadt, A.-K., Schmidt, L., Kuhn, C., Summ, M., Adams, M., Garbacenkaite, R., Leonhardt, E.,Reinhart, S., & Kerkhoff, G. (2014a). Perceptual re-learning of binocular fusion after hypoxic brain damage – four controlled single case treatment studies. *Neuropsychology, 28* (3), 382-387. DOI: 10.1037/neu0000019

Abstract

Objective: Hypoxic brain damage is characterized by widespread, diffuse-disseminated brain lesions, which may cause severe disturbances in binocular vision, leading to diplopia and loss of stereopsis, for which no evaluated treatment is currently available. The study evaluated the effects of a novel binocular vision treatment designed to improve binocular fusion and stereopsis as well as to reduce diplopia in patients with cerebral hypoxia.

Method: Four patients with severely reduced convergent fusion, stereopsis, and reading duration due to hypoxic brain damage were treated in a single-subject baseline design, with three baseline assessments before treatment to control for spontaneous recovery (pretherapy), an assessment immediately after a treatment period of 6 weeks (posttherapy), and two follow-up tests 3 and 6 months after treatment to assess stability of improvements. Patients received a novel fusion and dichoptic training using 3 different devices designed to slowly increase fusional and disparity angle.

Results: After the treatment, all 4 patients improved significantly in binocular fusion, subjective reading duration until diplopia emerged, and 2 of 4 patients improved significantly in local stereopsis. No significant changes were observed during the pretherapy baseline period and the follow-up period, thus ruling out spontaneous recovery and demonstrating long-term stability of treatment effects.

Conclusions: This proof-of-principle study indicates a substantial treatment-induced plasticity after hypoxia in the relearning of binocular vision and offers a viable treatment option. Moreover, it provides new hope and direction for the development of effective rehabilitation strategies to treat neurovisual deficits resulting from hypoxic brain damage.

[1] Zur Wahrung der Lizenzrechte der Verlage werden nachfolgend nur die Abstracts dargestellt. Die Originalartikel sind unter der jeweils angegebenen DOI abrufbar.

Appendix B:

Schaadt, A.- K., Schmidt, L., Reinhart, S., Adams, M., Garbacenkaite, R., Leonhardt, E., Kuhn, C., & Kerkhoff, G. (2014b). Perceptual Relearning of Binocular Fusion and Stereoacuity After Brain Injury. *Neurorehabilitation & Neural Repair, 28*(5), 462-471. DOI: 10.1177/1545968313516870

Abstract

Background. Brain lesions may disturb binocular fusion and stereopsis, leading to blurred vision, diplopia, and reduced binocular depth perception for which no evaluated treatment is currently available. Objective. The study evaluated the effects of a novel binocular vision treatment designed to improve convergent fusional amplitude and stereoacuity in patients with stroke or traumatic brain injury (TBI). Methods. Patients (20 in all: 11 with stroke, 9 with TBI) were tested in fusional convergence, stereoacuity, near/far visual acuity, accommodation, and subjective binocular reading time until diplopia emerged at 6 different time points. All participants were treated in a single subject baseline design, with 3 baseline assessments before treatment (pretherapy), an assessment immediately after a 6-week treatment period (posttherapy), and 2 follow-up tests 3 and 6 months after treatment. Patients received a novel fusion and dichoptic training using 3 different devices to slowly increase fusional and disparity angles. Results. At pretherapy, the stroke and TBI groups showed severe impairments in convergent fusional range, stereoacuity, subjective reading duration, and partially in accommodation (only TBI group). After treatment, both groups showed considerable improvements in all these variables as well as slightly increased near visual acuity. No significant changes were observed during the pretherapy and follow-up periods, ruling out spontaneous recovery and demonstrating long-term stability of binocular treatment effects. Conclusions. This proof-of-principle study indicates a substantial treatment-induced plasticity of the lesioned brain in the relearning of binocular fusion and stereovision, thus providing new, effective rehabilitation strategies to treat binocular vision deficits resulting from permanent visual cortical damage.

Appendix C:

Schaadt, A.-K., Brandt, S.A., Kraft, A., Kerkhoff, G. (2015). Holmes and Horrax (1919) revisited: Impaired binocular fusion as a cause of “flat vision” after right parietal brain damage – A case study. *Neuropsychologia, 69*, 31-38.
DOI: 10.1016/j.neuropsychologia.2015.01.029

Abstract

The complete loss of binocular depth perception ("flat vision") was first thoroughly described by Holmes and Horrax (1919), and has been occasionally reported thereafter in patients with bilateral posterior-parietal lesions. Though partial spontaneous recovery occurred in some cases, the precise cause(s) of this condition remained obscure for almost a century. Here, we describe a unique patient (EH) with a large right-sided occipito-parietal hemorrhage showing a complete loss of visual depth perception for several months post-stroke. EH could well simultaneously describe multiple visual objects - hence did not show simultanagnosia - but at the same time was completely unable to estimate their distance from him. In every 3-D visual scene objects appeared equidistant to him, thus experiencing a total loss of depth perception ("flat vision"). Neurovisual assessments revealed normal functions of the eyes. EH showed bilateral lower field loss and a severely impaired binocular convergent fusion, but preserved stereopsis. Perceptual re-training of binocular fusion resulted in a progressive and finally complete recovery of objective binocular fusion values and subjective binocular depth perception in a far-to-near-space, gradient-like manner. In parallel, visual depth estimation of relative distances improved, whereas stereopsis remained unchanged. Our results show that a complete loss of 3-D depth perception can result from an isolated impairment in binocular fusion. On a neuroanatomical level, this connection could be explained by a selective lesion of area V6/V6A in the medial occipito-parietal cortex that has been associated with the integration of visual space coordinates and sustained eye-positions into a cyclopean visual 3-D percept.