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Homonymous hemianopia before and after pediatric epilepsy surgery: prospective studies on identification, prevalence and adaptation

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Abbreviations

DTI   diffusion tensor imaging

fMRI   functional magnetic resonance imaging

MRI   magnetic resonance imaging

1 Introduction

1.1 Pharmaco-refractory epilepsy

Epilepsy is defined as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures (Fisher et al. 2014). It is one of the most common neuropediatric diseases. In Europe, the incidence in children and adolescents is estimated at 70/100,000 (Forsgren et al. 2005).

About one third of these patients suffers from pharmaco-refractory epilepsy (Anyanwu and Motamedi 2018). This means that epileptic seizures persist after adequate trials of at least two antiepileptic drugs which are tolerated and appropriately chosen and used in monotherapy or combination therapy (Kwan et al. 2010). Pharmaco-refractory epilepsy is also referred to in other ways, for example, as refractory, drug-resistant or medically-intractable epilepsy.

Even though the mechanisms underlying pharmaco-resistance in epilepsy are not completely understood, the pathogenesis is likely multifactorial. The type and severity of the underlying neuropathology are considered relevant factors in pharmaco-refractory epilepsy. Furthermore, it is hypothesized that increased expression and activity of efflux pumps of the blood-brain barrier can limit penetration of antiepileptic drugs to the seizure focus (Kwan 2000; Schinkel 1997). Alternative hypotheses suggest reduced drug sensitivity due to an epilepsy-induced alteration of cellular targets of antiepileptic drugs (Dalic and Cook 2016) or due to abnormal reorganization of neuronal circuitry (Kwan and Brodie 2002). Other researchers theorize that in some patients, autoimmune processes may play a role in the pathogenesis of pharmaco-refractory epilepsies (Palace and Lang 2000). Additional studies note that genetic variants of proteins that are involved in the pharmacokinetics and pharmacodynamics of antiepileptic drugs may be causal for pharmaco-resistance (Dalic and Cook 2016).

Recurrent seizures can lead to progressive structural damage of the nervous system as well as to impaired cognitive development in children (Bjørnaes et al. 2001). In addition, patients with pharmaco-refractory epilepsies have higher incidences of psychiatric illnesses such as depression and substance abuse. Adding to these burdens are social, educational and vocational disadvantages. These effects of pharmaco-refractory epilepsies are accompanied by reduced quality of life, and moreover by increased mortality and decreased life expectancy (Laxer et al. 2014).

Even if patients with pharmaco-refractory epilepsies represent the minority of the population with epilepsy, they require the overwhelming majority of time, effort and focus from their treating physicians (Laxer et al. 2014).

1.2 Pediatric epilepsy surgery

Epilepsy surgery is an effective treatment option for pharmaco-refractory epilepsy (Anyanwu and Motamedi 2018; Engel 2011; Téllez-Zenteno et al. 2005). This intervention aims at seizure freedom, insofar as the underlying neuropathology makes this achievable, or alternatively, at the reduction of frequency and severity of seizures. Moreover, epilepsy surgery can be conducted in order to cease or decrease the antiepileptic medication and to enhance neurodevelopment. The patients as well as their families strive for improved quality of life postoperatively.

Early surgical treatment in infants and young children has been recommended by researchers due to children's greater brain plasticity and the compensational capacity in childhood (Chugani et al. 1996; Gleissner et al. 2005). In preventing harmful consequences of uncontrolled epileptic seizures and drug therapy, early interventions may ameliorate brain development of severely impaired children (Bajer et al. 2019; Freitag and Tuxhorn 2005; Jonas et al. 2004; Jonas et al. 2005; Loddenkemper et al. 2007; Skirrow et al. 2011; Viggedal et al. 2013).

Epilepsy surgery requires a complex presurgical evaluation in an epilepsy center including confirmation of the diagnosis, classification of the seizure type and identification of the epileptogenic zone. The presurgical workup serves to evaluate the patient's suitability for surgical treatment and to define the most beneficial surgical approach (Anyanwu and Motamedi 2018).

In general, a complete resection of the epileptogenic zone provides the highest chances for postoperative seizure freedom, but the side effects of functional impairments increase with the extension of resection. Thus, the amount of cortex to resect (or disconnect) must be weighed against the risks and individualized in every patient.

In a majority of infants and young children with pharmaco-refractory epilepsies, a favorable seizure outcome can be achieved by epilepsy surgery. Seizure-free rates between 48% and 73% have been reported (Bittar et al. 2002; Duchowny et al. 1998; Dunkley et al. 2011; Loddenkemper et al. 2007; Ramantani et al. 2013; Reinholdson et al. 2015; Steinbok et al. 2009; Sugimoto et al. 1999; Wyllie et al. 1996). An established epilepsy surgery method is hemispherotomy, which is applied in patients with pharmaco-refractory epilepsies resulting from diffuse hemispheric diseases. In this surgical treatment, the complete hemisphere affected by severe epilepsy is disconnected from other areas of the nervous system. This functional isolation of the epileptogenic zone provides good seizure outcome, with seizure-free rates between 57% and 90% (Basheer et al. 2007; Palma et al. 2019; Panigrahi et al. 2016; Roth et al. 2017; Shimizu 2005). As hemispherotomy always produces hemiparesis and homonymous hemianopia on the contralesional side, it is principally considered in patients with preexisting motor and visual deficits. However, in some patients with good motor functions and / or intact visual field, the new acquisition of hemiparesis and / or hemianopia can be tolerated if the advantages of hemispherotomy outweigh these side effects.

1.3   Visual pathway

A large proportion of the brain serves visual function. The visual cortex, including the vision-associated areas, corresponds to approximately 55% of the entire cortical area in primates (Felleman and van Essen 1991; Moraes 2013; Prasad and Galetta 2011). The functional organization of the visual sensory system begins in the retina, where the first three neurons of the visual pathway are located. The first of these neurons are the retinal photoreceptor cells. There are two classes of photoreceptor cells, i.e. rods and cones, and these convert light energy into an electrochemical signal. This signal is passed to bipolar cells, which correspond to the second neuron, and then to ganglion cells, which are also known as the third neuron. The ganglion cell axons form the optic nerve, which carries visual information to the optic chiasm. Here, nasal fibers from each eye cross over to the opposite side of the brain, whereas temporal fibers remain on the same side. This semidecussation brings together fibers dealing with the same part of the visual field. Therefore, the optic tract carries fibers from both the ipsilateral temporal retina and the contralateral nasal retina to the lateral geniculate nucleus. In this specialized portion of the thalamus, the synapse to the fourth neuron is located. Information travels through the optic radiation, which fans out in the temporal and parietal lobes (►Figure 1). The optic radiation terminates in the primary visual cortex located in the occipital lobe, where the first analysis of visual information is performed (Joukal 2017; Kandel et al. 2000; Koenraads 2016; Moraes 2013; Prasad and Galetta 2011).

From the primary visual cortex, the ventral and dorsal streams carry information to extrastriate areas, where further processing takes place. The ventral stream projects from the occipital lobe to the temporal lobe and largely determines perceptual object identification including color, contrast and shape. This stream is therefore also called the "what pathway". In contrast, the dorsal stream passes from the occipital lobe to the parietal lobe and not only carries information about spatial features and movement but also mediates the required sensorimotor transformations for visually guided actions. The dorsal stream is also referred to as the "where pathway" (Goodale and Milner 1992; Joukal

2017). Ultimately, both dorsal and ventral streams send visual information to distant cortical areas for the highest levels of processing (Prasad and Galetta 2011). Even the proponents of this dualistic model, however, admit that it is an oversimplification of the true situation, given that strong interactions occur between the two networks (Terpening and Watson 2007).
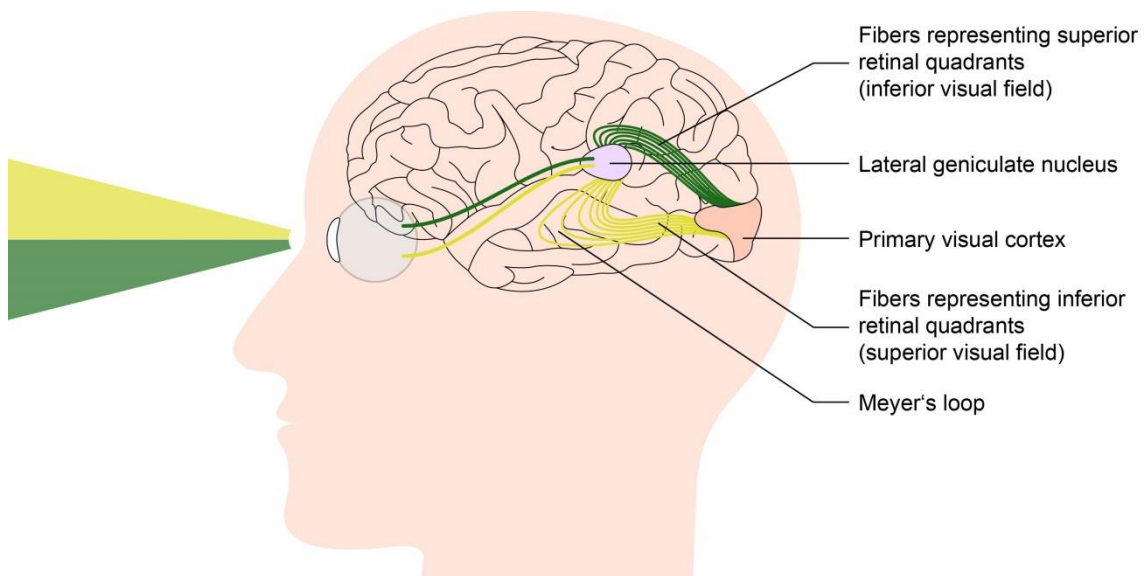
Figure 1: Course of the optic radiation. Source: Drawn by Kilian Weidig.

Fibers relaying input from the inferior part of the retina pass through the temporal lobe sweeping rostrally in a broad arc called Meyer's loop, which passes around the inferior horn of the lateral ventricle, and finally turning caudally to reach the occipital pole below the calcarine fissure. In contrast, fibers representing the superior part of the retina lie deep in the parietal lobe and travel straight back terminating in the occipital pole above the calcarine fissure.

1.4   Visual field defects in children

In children, lesions in the cerebral part of the visual pathway can stem from various conditions, such as genetic disorders, malformations, hypoxic-ischemic encephalopathies, infections, elevated intracranial pressure, drugs and toxins, hypoglycemia and other metabolic disorders, traumatic brain injuries, epileptic seizure disorders and also epilepsy surgery (Haaga et al. 2018; Koenraads 2016). These lesions can be located at various points along the visual pathway, resulting in specific visual field defects arising from the retinotopical organization of the visual pathway at all levels (►Figure 2).
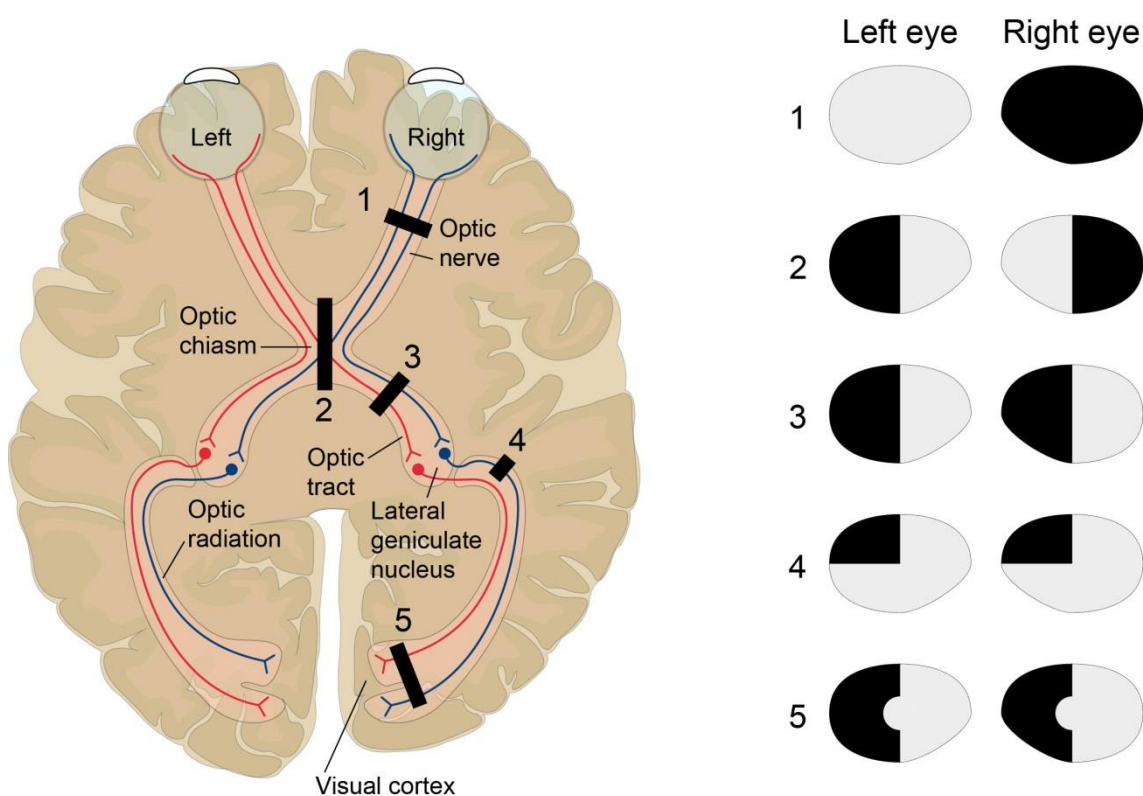
Figure 2: Visual field defects produced by lesions at various points along the visual pathway. Source: Drawn by Kilian Weidig.

As shown in (1), optic nerve lesions lead to total or partial loss of vision in the corresponding eye. Optic chiasm lesions, which are marked in (2), can be caused by space-occupying lesions around the sella turcica (e.g. pituitary tumours) and typically result in bitemporal hemianopia, meaning that vision is

missing in the temporal visual field halves of both the right and left eye. As represented in (3), optic tract lesions produce contralateral homonymous hemianopia, which means visual field loss of both eyes on the left or right side of the vertical midline. Damage along more medial parts of the optic radiation results in inferior homonymous quadrantanopia, while damage along more lateral parts of the optic radiation causes superior homonymous quadrantanopia on the contralesional side (4). Injury to the primary visual cortex can lead to a phenomenon called macular sparing, which is shown in (5). Macular sparing means the exception of foveal vision in homonymous hemianopia or homonymous quadrantanopia. The exact mechanism of macular sparing is still uncertain (Kolb and Whishaw 2009). One hypothesis is that the macular region of the visual cortex has a double blood supply from the middle cerebral artery and the posterior cerebral artery. If there is damage to one vascular pathway, there is still another artery which provides blood to the macular region of the visual cortex. This means that vision in the center of the visual field is preserved, whereas vision in peripheral areas is lost (Leff 2004).

Pediatric visual field defects can have serious consequences on a child's motor, emotional, social and psychological development (Koenraads 2016; van Hof-van Duin et al. 1998). Early identification of visual field defects is important for correct interpretation of a child's behavior, for parent counseling and for the timely initiation of appropriate rehabilitation. Moreover, visual field assessment can play a role in monitoring the progression of a brain disorder, in determining a child's prognosis, and in evaluating the presence of a visual field defect in children eligible for epilepsy surgery (Koenraads 2016).

For various reasons, visual field defects in children can be easily overlooked. First, vision is an internalized function. Compared to motor, verbal or cognitive dysfunctions, visual impairment including visual field loss is less obvious and might therefore be regarded as relatively less important in complex combinations of multiple disabilities (Harbert et al. 2012; Koenraads 2016).

Second, children with visual field defects often compensate well in daily life, so that they do not present typical problems like bumping into objects or people. Third, visual acuity testing may reveal normal results in children who have visual field defects due to retrogeniculate lesions, but only if the cortex representing the macula is intact. Additionally, pupillary light reflexes are normal, since fibers that subserve the light-pupillary reflex leave the optic tract and enter the brainstem before the lateral geniculate nucleus (Good et al. 1994).

Due to these missing clinical clues, special visual field assessment is required. In children with brain diseases, however, visual field testing is often challenging not only due to low cooperation and short attention span but also due to additional deficits caused by the brain lesions, such as motor and cognitive impairments. These hurdles in assessing the children in a useful manner often lead physicians to avoid such measurements. Available methods for pediatric visual field assessment are not widely used because they are relatively unknown.

1.5 Neuroimaging of visual field defects

Neuroimaging techniques can be of value to objectively predict or diagnose not only the presence but also the type of visual field defects in children. Neuroimaging is generally divided into two main categories, namely structural and functional imaging. Structural imaging aims at visualizing the various structures of the brain and any physical abnormalities that may affect them, whereas functional imaging measures activity in certain parts of the brain while the patient performs special tasks.

A widely-used structural brain imaging method is Magnetic Resonance Imaging (MRI). The most common MRI sequences are T1- and T2-weighted scans, which can visualize cortical areas and the white matter. MRI plays a role in identification of homonymous visual field defects as it serves to detect lesions of

the retrochiasmatic visual pathway (Haaga et al. 2018). In most cases, however, diagnosis of early acquired visual field defects cannot merely be based on structural MRI, but requires additional measures.

One of these additional measures is the Diffusion Tensor Imaging (DTI) technique, which is based on measuring the diffusion of water molecules. In brain tissue, molecular diffusion is not free, but reflects interactions with many obstacles, such as macromolecules, fibers and membranes. Water molecule diffusion patterns can therefore reveal microscopic details about tissue architecture (Basser et al. 1994; Pierpaoli et al. 1996). Fiber tractography uses diffusion tensor data to enable three-dimensional visualization of specific white matter fiber tracts like the optic radiation (Ciccarelli et al. 2005; O'Donnell and Westin 2011; Okada et al. 2007; Wu et al. 2012). Damage or displacement of fiber tracts can be visualized better than by conventional MRI (Lee et al. 2005). Therefore, DTI and fiber tractography are valuable diagnostic tools in the preoperative neurosurgical planning in order to protect relevant fiber tracts. (Reith 2015).

Functional magnetic resonance imaging (fMRI) of the brain provides images of changes both in local blood flow and in oxygenation that are evoked by neural activity. This technique is capable of identifying brain areas that respond not only to visual stimulation but also to the performance of vision-related tasks. fMRI allows retinotopic mapping, which represents the correspondence between the visual field and its representation in the visual cortex (Raz and Levin 2014; Wandell and Winawer 2010). Moreover, fMRI enables localization of higher visual functions in the occipital cortex (McFadzean et al. 1999). On visual field maps, fMRI information can be integrated with other measures, including electro-encephalography (EEG), magneto-encephalography (MEG) and electro-corticography (ECoG), in order to clarify spatial locations of the neural signals (Koenraads 2016; Wandell and Winawer 2010). Sophisticated DTI and fMRI measures can also provide insight into the mechanisms of cortical development and plasticity (Hoffmann and Dumoulin 2015).

1.6 Mechanisms of compensation and adaptation in children with homonymous hemianopia

Studies have shown that children with homonymous hemianopia can present characteristic mechanisms of compensation and adaptation. First, an anomalous head posture can occur. In turning the head to the side of the absent hemifield, children move the non-seeing field off to the side and center the seeing field (Donahue and Haun 2007; Good et al. 1994; Koenraads 2016; Paysse and Coats 1997; Zangemeister et al. 1982).

Anomalous head posture in patients with homonymous visual field defects is especially observable during tasks that require proper visual fixation (Koenraads 2016). The patient can be asked to fixate a small object or optotype positioned far away, while the examiner observes the head position of the patient in order to detect anomalous head posture including face turn (to the left or right), head tilt (to the left or right shoulder) or head tip (up or down).

Second, homonymous hemianopia in children is frequently accompanied by strabismus. Exotropia has been suggested as a compensational mechanism because it can expand the visual field equal to the angle of strabismic deviation (Bronstad et al. 2018; Donahue and Haun 2007; Herzau et al. 1988; Jacobson et al. 2012; Koenraads 2016; Levy et al. 1995; Saleh et al. 2006). Misalignment of the eyes results in diplopia or confusion, both of which can be prevented through anomalous retinal correspondence and suppression. These sensory adaptation mechanisms are more likely to develop in childhood (Bagolini 1967; Bronstad et al. 2018; Levy et al. 1995; Schor 2015).

Strabismus is mostly obvious and can be easily identified, but in some patients, misalignment of the eyes is barely detectable. It may help to shine a small light, such as a penlight, in the patient's eyes, and observe corneal light reflexes. When the position of both reflexes is symmetrical and located just slightly nasal to the center of the pupil, no strabismus is present. In contrast, asymmetrically positioned corneal light reflexes indicate the possibility of strabismus. Another method of determining the presence of strabismus is to use a cover test. In the

unilateral cover test, the patient focuses on an object, while the examiner covers one eye with an occluder and simultaneously observes the uncovered eye. In case of manifest strabismus, covering the fixating eye causes an eye movement in the deviating eye in order to look at the target. If the deviating eye is covered, there is no eye movement of the other eye because it is already fixating. In the alternate cover test, binocular vision is interrupted by alternately covering the right and left eye, making any form of latent and / or manifest strabismus visible (Kaufmann and Esser 2012).

Third, homonymous visual field defects can be compensated for by special eye movement strategies (Jacobson et al. 2012; Meienberg et al. 1981; Meienberg 1983; Pambakian et al. 2000; Tant et al. 2002; Zangemeister 1995; Zihl 1995a; Zihl 1999). These can be assessed in visual search tests.

1.7   Research questions

Specific neuroimaging findings as well as the clinical clues described above can raise suspicion of homonymous visual field defects in pediatric patients. Little is known, however, about the particular diagnostic and prognostic implications of these impairments in children. Focusing on pediatric epilepsy surgery patients, the scope of this thesis was (1) to study the prevalence and improve the identification of homonymous visual field defects, and (2) to investigate consequences and adaptation after surgically acquired new homonymous hemianopias.

1.7.1 Identification, assessment and prevalence of homonymous visual field defects in pediatric epilepsy surgery patients

The first study described in this thesis had three aims: First, to evaluate "campimetry" as a new examination method for visual field assessment in children. Second, to assess the prevalence of homonymous visual field defects

in pediatric epilepsy surgery patients. Third, to analyze strabismus and anomalous head posture as potential clinical signs for homonymous visual field defects. The clinical study is described in detail in the publication which forms the first part of the results section of this thesis.

1.7.2 Effects of surgically induced homonymous hemianopia on visual search in pediatric epilepsy surgery patients

During pediatric epilepsy surgery, one visual hemifield is sometimes sacrificed in the attempt to cure pharmaco-refractory epilepsies. These situations offer the unique chance to investigate the effects of a newly acquired homonymous hemianopia on visual search, using a prospective pre / post approach. This was the aim of the second study of this thesis. To our knowledge, this has never been done before; all previous publications on the effects of hemianopia have studied patients with unexpectedly acquired brain lesions, hence no pre-hemianopia data could be gathered. The clinical study is described in detail in the publication which forms the second part of the results section of this thesis.

2   Results

2.1   Study I: Uncovering homonymous visual field defects in candidates for pediatric epilepsy surgery (*Neumayr L, Pieper T, Kudernatsch M, Trauzettel-Klosinski S, Staudt M*, published in European Journal of Paediatric Neurology)

The first part of the results is formed by the printout of an article by Neumayr et al., which was published in *European Journal of Paediatric Neurology* in 2020. The following is the detailed bibliographic data of the publication:

Neumayr L, Pieper T, Kudernatsch M, Trauzettel-Klosinski S, Staudt M (2020) Uncovering homonymous visual field defects in candidates for pediatric epilepsy surgery. European Journal of Paediatric Neurology 25:165–171.

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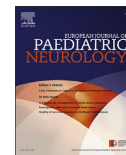
Original article

Uncovering homonymous visual field defects in candidates for pediatric epilepsy surgery

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ABSTRACT

Objectives: Perimetry in children can be challenging due to low cooperation and short attention span. Especially during the pre-surgical work-up of children with pharmaco-refractory epilepsies, however, diagnosing homonymous visual field defects (HVFDs) can be crucial for planning surgical strategies. Here, we evaluated "campimetry" for visual field testing in children. Furthermore, we analyzed strabismus and anomalous head posture as clinical signs for HVFDs.
Methods: Campimetry and a standard orthoptic examination were performed in 18 patients (age range: 3 y 2 m–18 y) who underwent epilepsy surgeries in our center during the study period, and in 11 additional patients (age range: 2 y 10 m–22 y 10 m) with suspected or confirmed HVFDs.
Results: In 16/18 patients of our unselected surgery cohort, pre- and postoperative campimetry was successfully completed. Of these, only 7/16 patients had intact visual fields pre- and postoperatively, while 5/16 patients already showed preoperative HVFDs and 4/16 patients suffered newly acquired HVFDs as calculated consequences of the surgery. Regarding clinical signs, strabismus (mostly esotropia) and anomalous head posture were specific indicators of HVFDs (strabismus: 6/12 with HVFDs vs 1/18 without; anomalous head posture: 8/12 with HVFDs vs 0/18 without).
Conclusions: For perimetry in children with limited cooperation, we suggest campimetry as it allows early detection and fast delineation of HVFDs. This is particularly important in pediatric epilepsy surgery patients, who display a surprisingly high proportion of HVFDs (9/16). Both, strabismus and anomalous head posture can indicate such HVFDs. Therefore, clinicians should pay attention to these clinical signs, especially in the context of epilepsy surgery.
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1. Introduction

Epilepsy surgery is an effective alternative treatment for pharmaco-refractory epilepsies.[1–3] In contrast to adults, who typically require circumscribed lesionectomies or standard temporal lobe resections, many children need multilobar resections, often involving the entire temporal and/or occipital lobes. Severe cases can even require hemispherotomies.[4–6] Such surgical treatments unavoidably result in contralateral hemianopias.

Some of these children have preexisting complete hemianopias due to brain lesions causing their epilepsies, so that resections or disconnections of the optic radiation or the visual cortex do not cause new deficits. In contrast, in children with preoperatively normal visual fields (or with incomplete hemianopias), the clinical team must discuss whether the chance to successfully treat the epilepsy justifies sacrificing one hemifield of vision. Hence, when making these decisions, it is crucial to know about any preexisting HVFDs in candidates for epilepsy surgery.

In cooperative adults, the visual field can be easily examined using conventional perimetry techniques. In children, perimetry presents a major challenge due to lower cooperation and shorter attention spans. Infants and toddlers as well as children who have deficits in cognition, behavior and attention are typical pediatric

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epilepsy surgery candidates, so that standard testing strategies demanding the patients' full cooperation and concentration are not feasible.

To date, no well-established perimetry technique exists for this cohort. In clinical practice, children's visual fields are usually assessed using confrontational perimetry. While this examination is quick and easy, it does not result in an accurate objective quantification of the visual field.[7]

Previous studies have developed and tested special perimetry methods for children.[7–28] All these methods have, however, specific disadvantages. In several of these procedures, confrontational behavioral methods were used.[9,11,12,14,18,19,21,22] These methods were easy to perform and to implement in clinical practice, but they were imprecise,[9,14,18,19,21,22] potentially intimidating[9,12,14,18,21] and/ or they required two examiners.[11,14,19,22] Some authors used eye tracking systems to observe patients' eye and head movements.[7,8,15–17,20,23] These technical devices were objective, but they often required high investments of time and money and could also be intimidating for children.[7,15,16,20] Others used perimetry with visual evoked potentials,[10,14,24–28] which, while it is objective, does not provide information about the actual perception of a stimulus. A special computer game for perimetry in children was well accepted, but, even when tested in healthy children, showed high inter-subject test variability.[13] The first aim of our study was to overcome the disadvantages of these previous perimetry methods by developing and evaluating "campimetry" as an easily applicable, child-friendly, quick, yet precise assessment for visual fields in the clinical setting.

The second aim of our study was to systematically analyze the value of strabismus and anomalous head posture as potential clinical signs for HVFDs in a clinical pediatric sample of candidates for epilepsy surgery. These clinical signs have been described for patients with HVFDs.[21,29–39] The recognition of such signs is important since, in contrast to clearly evident sequelae of brain lesions like motor dysfunction and mental retardation, the impairment of visual function, and especially visual field defects, can easily escape identification.[28] Early onset visual field defects are often well compensated, which hinders even experienced examiners in detecting them during clinical observation, because typical signs for hemianopias like bumping into objects do not occur.[32,40]

Hence, children could be deprived of interventions to mitigate epilepsy in some cases because of an unfounded fear of causing new HVFDs.

2. Patients and methods

Between September 2017 and May 2018, 25 German-speaking children and adolescents underwent epilepsy surgeries in our center (median age: 8 y 6 m; age range: 2 y 1 m–18 y 5 m); 13 further patients operated during this period did not understand German and were therefore excluded. Of these 25 patients, 7 were excluded because they did not understand any verbal commands or could not sit on a chair for more than 10 min. The remaining 18 patients in this "surgery cohort" (median age: 8 y 10.5 m; age range: 3 y 2 m–18 y) were supplemented by 11 additional patients (median age: 10 y; age range: 2 y 10 m–22 y 10 m) examined during the diagnostic phase with suspected or confirmed HVFDs, as reported by the clinical staff of the pediatric epilepsy surgery ward. Approval from the ethics committee of the Faculty of Medicine, University of Tuebingen, and informed written consent from all 29 participants and/or their legal guardians were obtained.

The 18 patients in the surgery cohort were examined before (median: 5 d) and after (median: 7.5 d) their operations as well as about six months later (median: 6 m; range: 5 m–10 m), while the additional 11 patients with suspected or confirmed HVFDs were examined only once. All examinations included campimetry as well as a standard orthoptic examination.

2.1. Campimetry

All children were examined binocularly using a custom-made campimeter (Fig. 1) which was modified after a prototype developed in the Vision Rehabilitation Research Unit, Centre for Ophthalmology, University of Tuebingen.[41] The examiner asked the patient to fixate on a central red spot of light on the plane surface of the campimeter. By pressing buttons on a keyboard in an individual chosen order and rate, the examiner briefly switched on white light points around the red fixation point (three white points of light per quadrant at 20° and 30° radius apart). Simultaneously, the eye movements of the patient were observed. When the examiner
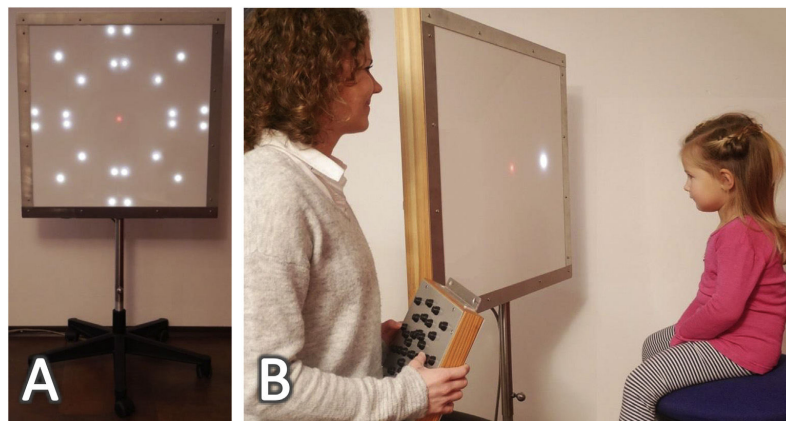
Fig. 1. (A) Campimeter. Around a central red fixation light, 24 white points of light are arranged (three per quadrant at 20° and 30° radius apart, respectively) (B) Campimetry examination situation. The patient is asked to fixate on the central spot of light. In random order, the examiner briefly switches on white light points and simultaneously observes the eye movements of the patient. The campimeter is positioned at a distance of 50 cm from the patient's corneal vertex, and its height is adjusted so that the patient is at eye level with the central red fixation light. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

noticed a directed eye movement of the patient towards the spot of light tested, the corresponding test point was marked as "perceived"; in the absence of an eye movement the test point was marked as "not perceived". The campimeter was positioned at a distance of 50 cm from the patients' corneal vertex, and its height was adjusted so that the patients were at eye level with the central red fixation light of the campimeter. A standard campimetry evaluation took 10–15 min.

2.2. Orthoptic examination

A trained orthoptist (LN) assessed the ocular alignment by means of corneal light reflexes and the cover test. These examinations were used to reveal strabismus such as intermittent or continuous exotropia or esotropia as well as vertical strabismus. Stereoscopic vision was checked with the Lang I Stereotest. In addition, the level of eye motility was determined. Finally, the orthoptist documented any anomalous head posture and nystagmus.

3. Results

3.1. Campimetry

Campimetry was tried in all 29 patients. Two of these did not cooperate sufficiently to perform campimetry (ages: 6 y 7 m and 10 y 3 m). These two patients were excluded from all further analyses, leaving 17 children in the surgery cohort and 10 in the cohort with suspected or confirmed HVFDs. Of these 27 patients, 25 could undergo the full examination, while in two (#4 and #5), we detected incomplete hemianopias but could not exactly specify it (ages: 11 y 5 m and 3 y 4 m). The demographic and clinical data of these 27 patients (median age: 9 y 1 m; age range: 2 y 10 m–22 y 10 m) as well as the results of campimetry and orthoptic examination are outlined in Table 1. The age distribution and examinability by the campimeter are shown in Fig. 2.

3.2. Prevalence of homonymous visual field defects

In the surgery cohort, the preoperative visual field was intact in 12/17 patients, while 5/17 patients had preexisting HVFDs (one complete hemianopia, four incomplete hemianopias). As patient #10 refused further examinations, the postoperative analysis includes only 16 patients. Postoperatively, of the five patients with preexisting HVFDs, the one complete hemianopia remained unchanged, while four incomplete hemianopias had been converted into complete hemianopias. Of the eleven patients without preexisting HVFDs, four had newly acquired complete hemianopias, while seven patients still had intact visual fields after the operation. All patients with newly acquired or worsened HVFDs had undergone planned occipital resections/disconnections or temporal resections involving the optic radiation; hence, all postoperative deteriorations were expected effects of the operations.

In the cohort with suspected or already known HVFDs, 7/10 patients had intact visual fields, while in 3/10 children we discovered or confirmed HVFDs (always complete hemianopias).

3.3. Clinical signs for visual field defects

Of the entire sample of 27 patients (both cohorts together), 26 could be analyzed for clinical signs: Patient #10 had to be excluded due to inability to comply with the orthoptic examination, and refused the postoperative examinations.

At the time of the first examination, 18/26 patients had intact visual fields. Of these, 17/18 showed neither strabismus nor anomalous head posture, and only 1/18 showed strabismus. The remaining 8/26 children had preexisting HVFDs. Of these, all patients with pre- or perinatally acquired ("congenital") HVFDs (5/5) presented both strabismus and anomalous head posture, while of the three patients with preexisting post-neonatally acquired HVFDs (here: 8 months or older), none showed strabismus, and only 1/3 had anomalous head posture.

In the surgery cohort, four patients with preoperatively intact visual fields sustained hemianopias as expected consequences of their epilepsy surgeries. One of these four patients (#6) postoperatively developed strabismus (exotropia) with diplopia (i.e., decompensated exophoria), which became intermittent (i.e., decompensating exophoria) six months later. Two patients developed anomalous head posture (still present after six months), and only one neither (Fig. 3). Of the four patients with preoperative incomplete hemianopias which converted into complete hemianopias, we observed anomalous head posture, deteriorating in patient #4 and developing anew in patient #5, but no change with respect to strabismus.

In total, our cohort comprised 12 patients with HVFDs (8 preexisting, 4 acquired by surgery). Of these, 6/12 patients showed strabismus - 5/6 had esotropia (one of them additionally dissociated vertical deviation) and 1/6 exotropia. In most cases, strabismus was contralateral to the side of the brain lesion (n = 4), rarer was ipsilateral (n = 1) or alternating (n = 1). Anomalous head posture was noted in 8/12 patients with HVFDs. This head posture had different presentations: 4/8 children turned their head in a horizontal plane to the side of the hemianopia, while 4/8 patients showed a head turn to the other side, a head tilt and/or chin-down. In only 1/17 patients with an intact visual field, a head tilt was noticed.

Thus, in this highly selected cohort of a pediatric epilepsy surgery service, strabismus was found more frequently in children with HVFDs (6/12 vs 1/18; p = 0.01, Fisher), and strabismus had a positive predictive value of 86%, negative predictive value of 74%, specificity of 94% and sensitivity of 50% for the presence of HVFDs. Similarly, anomalous head posture was found more frequently in children with HVFDs (8/12 vs 0/18; p < 0.001; Fisher), with a positive predictive value of 100%, a negative predictive value of 82%, a specificity of 100% and a sensitivity of 67%.

4. Discussion

Our study produced three major findings. First, the campimetry method we tested here yielded reliable information in a large proportion of pediatric epilepsy surgery patients: Despite the many problems of such patients in terms of cooperation, cognition and attention, campimetry was possible in 15/25 (60%) patients of an unselected cohort operated in our center during the study period. This data suggests that the test may be a valuable tool to detect HVFDs in young and/or cognitively impaired children. To our knowledge, this is the first study to evaluate the applicability of this device. The 24 white light points enable a more precise quantification of the visual field extent than do confrontational perimetry and other methods based on behavioral observation.[9,11,12,14,18,19,21,22] In contrast to other devices,[9,12,14–18,21,23] the patient is not restricted by the campimeter because it is a plane surface rather than an enclosure, and thus it is less intimidating. Furthermore, some previously described methods require both an examiner and an observer,[11,14,19,22] while campimetry is feasible with only one person. Compared to eye tracking systems,[7,8,15–17,20,23] our device is less expensive. Another advantage of campimetry is that this examination takes only a short time (approximately 5–15 min), which fits the children's short attention spans. Furthermore, the order of the test points can be variably chosen so that the examiner can adapt the

Table 1
Demographic and clinical data of all patients.

Pt #	Sex	Age at first examination (y;m)	Diagnosis	Age at onset of brain damage (y;m)	IQ	Preoperative VFD	Preoperative Strabismus	Preoperative AHP	Surgery	Age at surgery (y;m)	Postoperative VFD	Postoperative Strabismus	Postoperative AHP	Follow-up Strabismus	Follow-up AHP	
1	f	13;1	COL4A1 mutation, periventricular lesions L>R	congenital / 3y*	40	HeAn R, comp.	Esotropia R	Turn R	Hemispherotomy R	13;1	HeAn R, comp.	idem	idem	idem	idem	pre-existing VFD
2	f	5;8	PVH with venous infarction R	congenital	67	HeAn L, inc.	Eso- & Hypertropia L, DVD R/L	Tilt R	Hemispherotomy L	5;11	HeAn L, comp.	idem	idem	idem	idem	
3	f	3;2	Sturge Weber syndrome temp.-par.-occ. L	congenital	n/a**	HeAn R, inc.	Esotropia L	Turn R	Res. temp.-par.-occ. L	3;4	HeAn R, comp.	idem	idem	n/a	n/a	
4	f	11;5	PVL R>>L	congenital	n/a**	HeAn L, inc.	Esotropia L/alt.	Tilt L, chin-down	Hemispherotomy R	11;11	HeAn L, comp.	idem	idem + Turn L	n/a	n/a	
5	m	3;4	Subarachnoid hemorrhage & ischemic stroke fro.-temp. L	8m	n/a**	HeAn R, inc.	-	-	Hemispherotomy L	3;8	HeAn R, comp.	-	Turn R	-	idem	
6	m	18;0	Ganglioglioma temp. R	congenital	121	-	-	-	Res. temp.-occ. R	18;0	HeAn L, comp.	Esotropia alt.	idem	intermittent Exotropia	-	newly acquired VFD
7	f	8;5	PVH with venous infarction L	congenital	61***	-	-	-	Hemispherotomy L	8;8	HeAn R, comp.	-	Turn R	intermittent Exotropia	idem	
8	m	5;5	PVH with venous infarction L	congenital	72	-	-	-	Hemispherotomy L	5;7	HeAn R, comp.	-	Tilt R	-	idem	
9	f	9;0	MCA infarction R	congenital	59***	-	-	-	Hemispherotomy R	9;1	HeAn L, comp.	-	-	-	-	
10	m	3;9	Sturge Weber syndrome fro.-par. R	congenital	79	-	-	not examinable	Hemispherotomy R	3;9	n/a	n/a	n/a	n/a	n/a	
11	f	17;5	PHACE syndrome, hippocampal sclerosis, PMG temp. L	congenital	68	-	Exotropia & DVD L	-	Res. temp. L	17;5	-	idem	-	idem	-	no VFD
12	f	5;11	FCD fro. L	congenital	108	-	-	-	Res. fro. L	5;11	-	-	-	-	-	
13	f	7;8	Ganglioglioma temp. L	congenital	90	-	-	-	Res. temp. L	7;10	-	-	-	-	-	
14	f	8;5	FCD fro. L	congenital	73	-	-	-	Res. fro. L	8;6	-	-	-	-	-	
15	f	10;10	FCD fronto-par. L	congenital	67***	-	-	-	Res. fro. L	10;10	-	-	-	-	-	
16	m	17;10	Astrocytoma fro. L	congenital	74	-	-	-	Res. fro. L	17;10	-	-	-	-	-	
17	f	18;0	Cavernoma temp. R	congenital	103	-	-	-	Res. temp. R	18;0	-	-	-	-	-	
18	m	2;10	FCD temp.-par.-occ. L	congenital		HeAn R, comp.	Esotropia R	Turn R	no surgery							
19	m	13;10	Hemorrhagic stroke (AV-malformation) temp.-par.-occ. R	2y		HeAn L, comp.	-	Turn R								
20	f	8;3	Head injury with hemorrhage temp. L	4y		HeAn R, comp.	-	-								
21	f	6;9	FCD temp. L	congenital		-	-	-								
22	m	22;10	FCD temp. L	congenital		-	-	-								
23	m	8;2	MCA infarction R	congenital		-	-	-								
24	m	10;0	Benign tumor temp. R	congenital		-	-	-								
25	m	10;2	MCA infarction L	congenital		-	-	-								
26	f	10;7	MCA infarction L	congenital		-	-	-								
27	f	7;4	Tumor & hemorrhage temp. L	2y		-	-	-								

*In patient #1, it cannot be decided whether the congenital brain lesion had already lead to hemianopia, or whether hemianopia only occurred as a consequence of a temporo-parieto-occipital resection at the age of 3 years.
Three more patients had undergone epilepsy surgeries before entering the study, at the age of 8 years (#6), 7 and 8 years (#15) and 14 years (#16) – none of which had had effects on the visual fields, however.
** Patients #3, #4 and #5 are clinically diagnosed with moderate cognitive impairment (i.e., IQ estimated between 35 und 49).
*** Patients #7, #9 and #15 showed highly significant differences between the performance intelligence quotient (PIQ) and the verbal intelligence quotient (VIQ). #7: PIQ 58, VIQ 72. #9: PIQ 54, VIQ 71. #15: PIQ 67, VIQ 82.
Abbreviations: AHP, anomalous head posture; alt., alternating; comp., complete; DVD, dissociated vertical deviation; f, female; FCD, focal cortical dysplsia; fro., frontal; HeAn, hemianopia; inc., incomplete; IQ, intelligence quotient; L, left; m, male; MCA, middle cerebral artery; n/a, not available; occ., occipital; par., parietal; PHACE, posterior fossa anomalies, hemangioma, arterial anomalies, cardiac anomalies and eye anomalies; PMG, polymicrogyria; PVH, periventricular hemorrhage; PVL, periventricular leucomalacia; R, right; res., resection; temp., temporal; VFD, visual field defect.
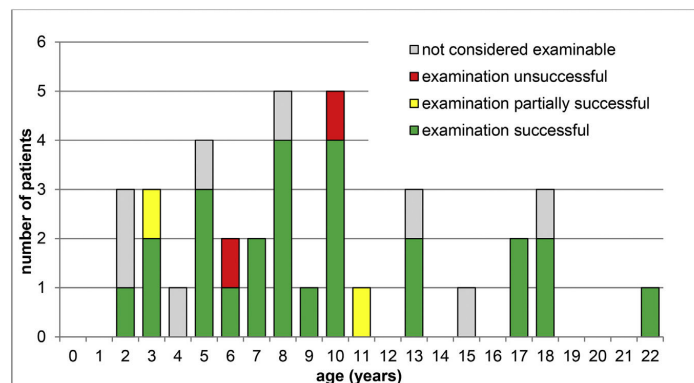
Fig. 2. Age distribution and examinability by the campimeter. The two patients with partially successful examinations (#4 and #5; in yellow) showed incomplete hemianopias, which could not be exactly outlined further. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article).
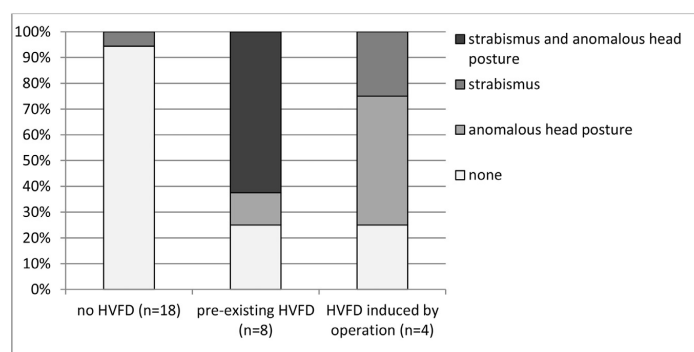

Fig. 3. Strabismus and anomalous head posture in patients with and without homonymous visual field defects (HVFDs). Note that the preoperative data of the four patients with "HVFD induced by operation" (right column) are included in the left column ("no HVFD") as well; hence, the numbers do not sum up to the total number of patients in the study. Preoperatively, these four patients showed neither strabismus nor anomalous head posture.

sequence to the patients' reactions. Hemianopia and quadrantanopia can be effectively detected by campimetry, but the method is suitable neither for scotomas nor for peripheral visual field loss due to the 30° radius external examination border. Campimetry represents the central 30° radius which is estimated to be the part of the visual field that is mainly used in everyday life.[42]

Second, we found an unexpectedly high prevalence of HVFDs in pediatric epilepsy surgery patients. Preoperatively, we found intact visual fields in 12/17 patients (71%), which is notably higher than the proportion of children with preoperatively intact visual fields in previous studies, ranging between 21% and 36%.[4,33,34,43] Postoperatively, 9 of our 16 patients were hemianopic (four of which as calculated and accepted consequences of the surgeries). This highlights the importance of following up on this issue in pediatric epilepsy surgery departments. Ivanov et al. emphasized the necessity of rehabilitation in cases with newly acquired visual field defects and investigated the effect of a computer-based visual search training as a new rehabilitation approach for children with homonymous hemianopia.[44]

Third, we confirmed strabismus and anomalous head posture as valuable clinical indicators for HVFDs in an epilepsy surgery setting, with positive predictive values of 86% and 100%, respectively.

Strabismus in our cohort was typically detected in patients with hemianopias due to congenital brain lesions (5/5 vs 1/7 with later-acquired hemianopias), and in these surprisingly always as esotropia, although this seems to be functionally unfavorable. In contrast, the many previous studies[21,29,30,32,33,35–37,45] on strabismus in patients with HVFDs reported mostly exotropia.

Several authors have suggested exotropia to the side of the homonymous visual field defect as a compensatory mechanism because it leads to functional enlargement of the binocular visual field when it is accompanied by an anomalous retinal correspondence and "panoramic vision".[30,32,33,36] In our cohort, exotropia was only found postoperatively in one patient (#6), who had normal retinal correspondence and thus suffered from diplopia. Therefore, we do not consider exotropia as a compensatory mechanism in this patient, nor could we find evidence supporting this hypothesis in the rest of our cohort. We suggest insufficient fusion due to the HVFDs as a possible explanation for strabismus in our patients; moreover, insufficient development of binocularity and also the underlying structural brain damage might be further explanations for this phenomenon. The latter is in accordance with Good et al., who proposed that exotropia occurs coincidentally as a consequence of neurological damage.[21]

Anomalous head posture was discovered in 8/12 patients with HVFDs. This association has already been reported in several studies.[21,31,33,36,38,39] Turning one's head to the side of the blind hemifield is considered a compensatory mechanism as it centers the residual visual field together with eye movements.[21,46] This head posture could also be of benefit for exploring the blind hemifield when making saccades to this side.[31–33,36] Our findings are consistent with these theories insofar as 4/8 patients with anomalous head posture did indeed turn their heads to the side of HVFDs. It remains unclear, however, why four other patients showed different anomalous head postures like a head-tilt or a turn towards the seeing hemifield.

Admittedly, our study has several limitations. Given the small sample size, caution must be taken in generalizing the results. There was also no differential verification of campimetry, such as comparison of our results with different perimetry methods. The only validation comes from the patients who suffered hemianopias as consequences of epilepsy surgeries: In all eleven patients, campimetry confirmed this anatomically unquestionable visual field defect. In very young patients, however, the results of campimetry may be less reliable than in older children. An additional drawback of our study is that reproducibility was not tested in each campimetry examination. In the 14 patients who underwent follow-up examinations, the findings of the postoperative campimetry could be confirmed. Inter-subject test variability, however, was evaluated neither in preoperative campimetry nor in any of the examinations of patients who did not undergo epilepsy surgery. Furthermore, the orthoptist who performed the campimetry as well as the orthoptic examinations was aware of the children's clinical backgrounds and (suspected) pathologies, which may have influenced the examination results. Additionally we cannot exclude that strabismus and anomalous head posture might have developed after our six-month follow-up period. Indeed, Koenraads et al. described strabismus and anomalous head posture occurring only after the first postoperative year in 8/17 and 11/24 children who underwent hemispherectomy, respectively.[33] Finally, the unexpectedly high predictive value of strabismus for HVFDs in our cohort must be assumed to arise from the fact that this selected cohort is comprised of almost exclusively children with focal brain lesions and can by no means be generalized to the general pediatric population.

4.1. Clinical implications of our study

HVFDs must be expected in many candidates for pediatric epilepsy surgery. In these children, however, obtaining valid information about visual fields represents a major challenge and requires an appropriate examination method. We suggest campimetry as it allows early detection and fast delineation of HVFDs. Campimetry is easy to establish in everyday clinical practice, it requires low investments in time and personnel and it can be reliably performed in most children, including toddlers.

In such children, any kind of strabismus and/or anomalous head posture can indicate HVFDs. Consequently, it is crucial that clinicians pay attention to these clinical signs. Their detection in the context of epilepsy surgery requires visual field assessment.

Declaration of Competing Interest

None.

Acknowledgements

References

1 C. Anyanwu, G.K. Motamedi, Diagnosis and surgical treatment of drug-resistant epilepsy, Brain Sci 8 (4) (2018).
2 J. Engel, Another good reason to consider surgical treatment for epilepsy more often and sooner, Arch Neurol 68 (6) (2011) 707–708.
3 J.F. Téllez-Zenteno, R. Dhar, S. Wiebe, Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis, Brain 128 (Pt 5) (2005) 1188–1198.
4 S.N. Basheer, M.B. Connolly, A. Lautzenhiser, E.M.S. Sherman, G. Hendson, P. Steinbok, Hemispheric surgery in children with refractory epilepsy: seizure outcome, complications, and adaptive function, Epilepsia 48 (1) (2007) 133–140.
5 J.-S. Kim, E.-K. Park, K.-W. Shim, D.S. Kim, Hemispherotomy and functional hemispherectomy: indications and outcomes, J Epilepsy Res 8 (1) (2018) 1–5.
6 J. Roth, S. Nagar, S. Constantini, I. Fried, HEMISPHEROTOMY for treatment OF refractory epilepsy IN children, Harefuah 156 (8) (2017) 482–485.
7 P. Satgunam, S. Datta, K. Chillakala, K.R. Bobbili, D. Joshi, Pediatric perimeter-A novel device to measure visual fields in infants and patients with special needs, Transl. Vis. Sci. Technol. 6 (4) (2017) 3.
8 L.E. Allen, M.E. Slater, R.V. Proffitt, E. Quarton, A. Pelah, A new perimeter using the preferential looking response to assess peripheral visual fields in young and developmentally delayed children, J. AAPOS 16 (3) (2012) 261–265.
9 V. Dobson, A.M. Brown, E.M. Harvey, D.B. Narter, Visual field extent in children 3.5-30 months of age tested with a double-arc LED perimeter, Vis Res 38 (18) (1998) 2743–2760.
10 G.F.A. Harding, E.L. Spencer, J.M. Wild, M. Conway, R.L. Bohn, Field-specific visual-evoked potentials: identifying field defects in vigabatrin-treated children, Neurology 58 (8) (2002) 1261–1265.
11 Y. Koenraads, K.P.J. Braun, D.C.P. van der Linden, S.M. Imhof, G.L. Porro, Perimetry in young and neurologically impaired children: the behavioral visual field (BEFIE) screening test revisited, JAMA Ophthalmol. 133 (3) (2015) 319–325.
12 D.L. Mayer, A.B. Fulton, M.F. Cummings, Visual fields of infants assessed with a new perimetric technique, Invest Ophthalmol Vis Sci 29 (3) (1988) 452–459.
13 M.A. Miranda, D.B. Henson, C. Fenerty, S. Biswas, T. Aslam, Development of a pediatric visual field test, Transl Vis Sci Technol 5 (6) (2016).
14 G. Mohn, J. van Hof-van Duin, Behavioural and electrophysiological measures of visual functions in children with neurological disorders, Behav Brain Res 10 (1) (1983) 177–187.
15 I. Murray, A. Perperidis, H. Brash, L. Cameron, A. McTrusty, B. Fleck, et al., Saccadic Vector Optokinetic Perimetry (SVOP): a novel technique for automated static perimetry in children using eye tracking, Conf Proc IEEE Eng Med Biol Soc 2013 (2013) 3186–3189.
16 I.C. Murray, L.A. Cameron, A.D. McTrusty, A. Perperidis, H.M. Brash, B.W. Fleck, et al., Feasibility, accuracy, and repeatability of suprathreshold saccadic vector optokinetic perimetry, Transl Vis Sci Technol 5 (4) (2016) 15.
17 J.J.M. Pel, M.C.M. van Beijsterveld, G. Thepass, J. van der Steen, Validity and repeatability of saccadic response times across the visual field in eye movement perimetry, Transl Vis Sci Technol 2 (7) (2013) 3.
18 G.E. Quinn, V. Dobson, R.J. Hardy, B. Tung, D.L. Phelps, E.A. Palmer, Visual fields measured with double-arc perimetry in eyes with threshold retinopathy of prematurity from the cryotherapy for retinopathy of prematurity trial. The CRYO-Retinopathy of prematurity cooperative group, Ophthalmology 103 (9) (1996) 1432–1437.
19 M.D. Sheridan, The STYCAR graded-balls vision test, Dev Med Child Neurol 15 (4) (1973) 423–432.
20 V. Tailor, S. Glaze, H. Unwin, R. Bowman, G. Thompson, A. Dahlmann-Noor, Saccadic vector optokinetic perimetry in children with neurodisability or isolated visual pathway lesions: observational cohort study, Br J Ophthalmol 100 (10) (2016) 1427–1432.
21 W.V. Good, J.E. Jan, L. DeSa, A.J. Barkovich, M. Groenveld, C.S. Hoyt, Cortical visual impairment in children, Surv Ophthalmol 38 (4) (1994) 351–364.
22 A.J. Hermans, J. van Hof-van Duin, A.M. Oudesluys-Murphy, Visual outcome of low-birth-weight infants (1500-2500 g) at one year of corrected age, Acta Paediatr 83 (4) (1994) 402–407.
23 I.C. Murray, B.W. Fleck, H.M. Brash, M.E. Macrae, L.L. Tan, R.A. Minns, Feasibility of saccadic vector optokinetic perimetry: a method of automated static perimetry for children using eye tracking, Ophthalmology 116 (10) (2009) 2017–2026.
24 A.I. Klistorner, S.L. Graham, J. Grigg, C. Balachandran, Objective perimetry using the multifocal visual evoked potential in central visual pathway lesions, Br J Ophthalmol 89 (6) (2005) 739–744.
25 Y.-J. Kim, E. Yukawa, K. Kawasaki, H. Nakase, T. Sakaki, Use of multifocal visual evoked potential tests in the objective evaluation of the visual field in pediatric epilepsy surgery, J Neurosurg 104 (3 Suppl) (2006) 160–165.

26 E.L. Spencer, G.F.A. Harding, Examining visual field defects in the paediatric population exposed to vigabatrin, Doc Ophthalmol 107 (3) (2003) 281–287.

27 E. Yukawa, Y.-J. Kim, K. Kawasaki, F. Taketani, Y. Hara, A child with epilepsy in whom multifocal VEPs facilitated the objective measurement of the visual field, Epilepsia 46 (4) (2005) 577–579.

28 E. Yukawa, T. Matsuura, Y.-J. Kim, F. Taketani, Y. Hara, Usefulness of multifocal VEP in a child requiring perimetry, Pediatr Neurol 38 (5) (2008) 360–362.

29 G.M. Saleh, S. Sivaprasad, C.J. Hammond, Homonymous hemianopia and exotropia: an important management issue, Eye 20 (12) (2006) 1402–1404.

30 Y. Levy, J. Turetz, D. Krakowski, B. Hartmann, P. Nemet, Development of compensating exotropia with anomalous retinal correspondence after early infancy in congenital homonymous hemianopia, J Pediatr Ophthalmol Strabismus 32 (4) (1995) 236–238.

31 E.A. Paysse, D.K. Coats, Anomalous head posture with early-onset homonymous hemianopia, J Am Assoc Pediatr Ophthalmol Strabismus 1 (4) (1997) 209–213.

32 L. Jacobson, F. Lennartsson, T. Pansell, G. Oqvist Seimyr, L. Martin, Mechanisms compensating for visual field restriction in adolescents with damage to the retro-geniculate visual system, Eye 26 (11) (2012) 1437–1445.

33 Y. Koenraads, D.C.P. van der Linden, M.M.J. van Schooneveld, S.M. Imhof, P.H. Gosselaar, G.L. Porro, et al., Visual function and compensatory mechanisms for hemianopia after hemispherectomy in children, Epilepsia 55 (6) (2014) 909–917.

34 A.N.V. Moosa, L. Jehi, A. Marashly, G. Cosmo, D. Lachhwani, E. Wyllie, et al., Long-term functional outcomes and their predictors after hemispherectomy in 115 children, Epilepsia 54 (10) (2013) 1771–1779.

35 V. Herzau, I. Bleher, E. Joos-Kratsch, Infantile exotropia with homonymous hemianopia: a rare contraindication for strabismus surgery, Graefes Arch Clin Exp Ophthalmol 226 (2) (1988) 148–149.

36 S.P. Donahue, A.K. Haun, Exotropia and face turn in children with homonymous hemianopia, J Neuro Ophthalmol 27 (4) (2007) 304–307.

37 S. Gamio, N. Melek, When the patient says no. Management of exotropia with hemianopic visual field defects, Binocul Vis Strabismus Q 18 (3) (2003) 167–170.

38 G. Porro, D. van der Linden, O. van Nieuwenhuizen, D. Wittebol-Post, Role of visual dysfunction in postural control in children with cerebral palsy, Neural Plast 12 (2–3) (2005) 205–210, discussion 263-72.

39 W.H. Zangemeister, O. Meienberg, L. Stark, W.F. Hoyt, Eye-head coordination in homonymous hemianopia, J Neurol 226 (4) (1982) 243–254.

40 F. Tinelli, A. Guzzetta, C. Bertini, D. Ricci, E. Mercuri, E. Ladavas, et al., Greater sparing of visual search abilities in children after congenital rather than acquired focal brain damage, Neurorehabilitation Neural Repair 25 (8) (2011) 721–728.

41 M. Haaga, S. Trauzettel-Klosinski, A. Krumm, S. Küster, I. Ivanov, A. Cordey, et al., Homonymous hemianopia in children and adolescents: an MRI study, Neuropediatrics 49 (2) (2018) 142–149.

42 J.E. Lovie-Kitchin, G.P. Soong, S.E. Hassan, R.L Woods, Visual field size criteria for mobility rehabilitation referral, Optom Vis Sci 87 (12) (2010) E948–E957.

43 A.M. Devlin, Clinical outcomes of hemispherectomy for epilepsy in childhood and adolescence, Brain 126 (3) (2003) 556–566.

44 I.V. Ivanov, S. Kuester, M. MacKeben, A. Krumm, M. Haaga, M. Staudt, et al., Effects of visual search training in children with hemianopia, PLoS One 13 (7) (2018), e0197285.

45 S.E. Handley, F. Vargha-Khadem, R.J. Bowman, A. Liasis, Visual function 20 Years after childhood hemispherectomy for intractable epilepsy, Am J Ophthalmol 177 (2017) 81–89.

46 J.C. Horton, M. Fahle, T. Mulder, S. Trauzettel-Klosinski, Adaptation, perceptual learning, and plasticity of brain functions, Graefes Arch Clin Exp Ophthalmol 255 (3) (2017) 435–447.

2.2 Study II: Sacrificing one visual hemifield during pediatric epilepsy surgery: effects on visual search (*Neumayr L, Gschaidmeier A, Trauzettel-Klosinski S, Pieper T, Kudernatsch M, Hofer W, Bajer C, Staudt M*, published in European Journal of Paediatric Neurology)

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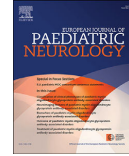
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Sacrificing one visual hemifield during pediatric epilepsy surgery: Effects on visual search

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ABSTRACT

Objectives: To investigate early and late effects of planned surgically acquired homonymous hemianopias on visual search in children and adolescents.
Methods: This prospective study included five patients (5y 5 m–18y 0 m; 2 girls) with pharmaco-refractory epilepsies in whom one visual hemifield was sacrificed as part of the surgical strategy, and, as controls, seven patients (5y 11 m–18y 0 m; 6 girls) undergoing epilepsy surgeries not affecting the visual fields. Visual search was studied using the "Table Test", which is an everyday life-like visual search test. General processing speed was studied using a standard IQ subtest.
Results: All five patients with newly acquired homonymous hemianopias showed a relative disadvantage of visual search times for objects in their newly blind hemifields immediately after the surgery. Six months later, this relative disadvantage had recovered completely in all patients. Nevertheless, compared with the preoperative situation, overall search times were still prolonged in the hemianopic patients, but this effect could be mitigated or even overcompensated by improvements in processing speed.
Conclusions: Children with homonymous hemianopias inflicted by epilepsy surgery develop effective compensation strategies to minimize the relative disadvantage of visual search in their blind hemifields. For changes in overall visual search times between the preoperative and the six-month follow-up examination, we could demonstrate overlapping effects of (a) deterioration by hemianopia and (b) amelioration by improved processing speed as part of the cognitive improvements achieved by amelioration of the epilepsy.

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1. Introduction

Visual search refers to the ability to find a target among simultaneously presented distractors. This demanding cognitive task depends on both visual sensory perception and visual processing speed. Impairments in these skills can lead to reduced visual search performance [1].

Retrochiasmal damage of the visual pathway causes contralesional homonymous hemianopia, which can impair spatial integration of visual information processing. Hence, visual search disorders can arise, i.e. difficulties in finding objects in the visual space corresponding to the affected field [2–5]. For obvious reasons, however, all previous studies share the problem that no behavioral data could be obtained from the period before the hemianopia had occurred, i.e. when the patients still had intact visual fields.

In our prospective study, we collected five patients with the rare situation of planned surgically acquired homonymous hemianopias in patients with pre-operatively intact visual fields. In all five patients, resective or disconnective surgeries were performed in order to relief the patients from pharmaco-refractory epilepsies, knowingly sacrificing one visual hemifield during this attempt. These rare situations provide a unique chance to perform a pre/post analysis of the consequences of a newly acquired hemianopia for visual search and their compensation. A similar approach has been chosen by Koenraads et al. [6], focusing on ophthalmological findings − including visual fixation, acuity and compensatory mechanisms − in

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a cohort of 45 children who underwent hemispherectomy, of whom many were tested before and after surgery and some had no pre-surgical hemianopia. In this study, the majority of children had a good visual outcome after hemispherectomy. It was shown that these children frequently develop anomalous head posture and exotropia as part of a coping strategy. [6].

2. Patients and methods

Twelve sufficiently cooperative patients (5y − 18y; 8 girls) with preoperatively intact visual fields receiving epilepsy surgeries in our center were included. The "study group" consisted of five patients with planned postoperative hemianopias, the "control group" of seven patients with postoperatively intact visual fields (►Table 1). Apart from patient #28, all participating subjects had also been included in a study on the detection of visual field defects in pediatric epileptic patients, during which they received assessments of their visual fields by campimetry. In this study [7], strabismus and anomalous head posture, which can serve as compensation mechanisms for homonymous hemianopia, were examined in 12 patients with homonymous visual field defects. Of these, strabismus was found in 6/12 patients and anomalous head posture was detected in 8/12 patients [7]. In the present study, postoperative changes in these compensatory strategies were detected in three patients: Patient #6 had developed exotropia, while patients #7 and #8 had developed anomalous head posture. Here, we used the same patient numbers to allow their cross-identification in this previous publication. After the surgeries inflicting new hemianopias, all five patients in the "study group" underwent several weeks of individualized inpatient rehabilitation with a special focus on the new hemianopia and/or performed a computerized saccade training program [8] (►Table 1). It was shown in a previous study that computerized saccade training improved search time in children with hemianopia [8]. To analyze the effects of these interventions was, however, not the aim of this study. Approval from the local ethics committee and informed consent were obtained.

Visual search was studied using the Table Test [9] before the surgeries (median, 5 d; range, 1−85 d), several days after the surgeries (median, 7.5 d; range, 6−13 d) and about six months later (median, 6 months; range, 5−10 months) (►Fig. 1A and B).

Postoperative changes in visual search times might, however, not only be caused by changes in vision (here: hemianopia), but also by altered cognitive parameters. Hence, we also analyzed processing speed using the Zahlen-Symbol-Test (in English IQ tests: "coding") of the Hamburg-Wechsler-Intelligenz Test für Kinder (HAWIK) Version III or the Hamburg-Wechsler-Intelligenz Test für Erwachsene (WIE). These data were obtained before (median, 5 d; range, 1−70 d) and about six months after the surgeries (median, 6 months; range, 5−6 months). The test results are given as raw values between 0 and 119 (<17 years olds) or 133 (≥17 years olds), higher values representing higher processing speed.

3. Results

In all twelve patients studied, epilepsy surgeries went without complications. At the time of the follow-up examination, antiepileptic medication had already been reduced in 4/12 patients, remained the same in 6/12 patients, while in patients #14 and #17, additional drugs had been introduced due to ongoing seizures after epilepsy surgery. The demographic and clinical data as well as the medication are outlined in ►Table 1.

Table 1
Demographic and clinical data. Patients are numbered as in our previous study [7]; patient #28 was recruited anew. The top five patients suffered hemianopias as calculated consequences of their epilepsy surgeries ("study group"), the bottom seven patients had surgeries not involving the visual system ("control group"). [1]Age at first examination; [2]Table Test overall median search times (affected half-field/intact half-field/both half-fields); [3]Engel classification. Abbreviations: BCT, brivaracetam; CBD, cannabidiol oil; CLB, clobazam; CST, computerized saccade training program; f, female; FCD, focal cortical dysplasia; fro., frontal; HeAn, Hemianopia; HRO, hemispherotomy; IR, inpatient rehabilitation with special focus on hemianopia, L, left; LAC, lacosamide; LEV, levetiracetam; LTG, lamotrigine; m, male/months; MCA, middle cerebral artery; n.a., not available (due to young age); occ., occipital; OXC, oxcarbazepine; par., parietal; PGB, pregabalin; PHT, phenytoin; R, right; Res., resection; RFA, rufinamide; STM, sulthiame; temp., temporal; TPM, topiramate; TT, Table Test; VGB, vigabatrine; VPA, valproate; y, years; ZST, Zahlen-Symbol-Test (measuring processing speed); ↓, reduced dosage.

| Pt #	Sex	Age [1] (y; m)	Diagnosis	Preoperative			Type of surgery	Postoperative		Follow-up (~6 months)				Seizure outcome [3]
				ZST raw value	TT median search time [2] (s)	Medication		TT median search time [2] (s)	Rehabili- tation	HeAn	ZST raw value	TT median search time [2] (s)	Medication	
6	m	18; 0	Ganglioglioma temp. R	97	1.3/1.2/1.3	LTG	Res. temp. R	2.9/1.3/1.7	IR + CST	L	80	2.4/1.6/1.9	unchanged	1 A
7	f	8; 5	Perinatal MCA infarct L	19	1.3/2.0/1.6	CBD LTG STM	HRO L	2.7/1.4/1.9	IR	R	24	2.2/4.0/3.0	CBD LTG ↓ STM	1 A
8	m	5; 5	Intraventricular hemorrhage L	n.a.	3.2/1.7/1.8	CLB OXC	HRO L	3.9/1.4/2.6	IR + CST	R	n.a.	2.1/2.2/2.2	OXC	1 A
9	f	9; 0	Perinatal MCA infarct R	8	2.3/1.4/2.0	STM	HRO R	2.3/1.2/1.5	CST	L	25	1.6/1.6/1.6	unchanged	1 A
28	m	11; 1	Cavernomas occ. R	38	1.5/1.1/1.4	OXC	Res. temp.-occ. R	1.8/1.4/1.6	IR + CST	L	45	1.4/1.8/1.5	unchanged	1 B
11	f	17; 5	Hippocampal sclerosis L, polymicrogyria temp. L	57	1.3/1.3/1.3	LTG	Res. temp. L	1.3/1.2/1.3		−	72	1.1/1.0/1.0	unchanged	1 A
12	f	5; 11	FCD fro. L	n.a.	1.2/1.4/1.3	OXC PHT	Res. fro. L	1.6/1.5/1.6		−	n.a.	1.7/1.2/1.5	OXC PHT ↓	1 A
13	f	7; 8	Ganglioglioma temp. L	43	1.0/1.0/1.0	LAC OXC	Res. temp. L	1.2/1.1/1.1		−	44	1.0/0.8/0.9	OXC	1 B
14	f	8; 5	FCD fro. L	23	1.9/1.2/1.5	CLB LAC OXC	Res. fro. L	1.6/1.4/1.5		−	24	1.4/1.4/1.4	LAC OXC VGB VPA	4 B
15	f	10; 10	FCD fronto-centro-par. L	24	1.8/1.1/1.5	LAC PGB PHT RUF	Res. fro. L	n.a.		−	30	1.1/1.5/1.1	unchanged	4 A
16	m	17; 10	Astrocytoma fronto-par. L	53	1.5/1.2/1.3	LAC LEV	Res. fro.-par. L	1.3/1.1/1.2		−	59	1.1/0.9/1.0	unchanged	1 A
17	f	18; 0	Cavernoma temp. R	67	1.2/1.1/1.1	LEV OXC TPM	Res. temp. R	1.1/1.1/1.1		−	79	0.9/0.9/0.9	BCT OXC ↓ TPM	2 B

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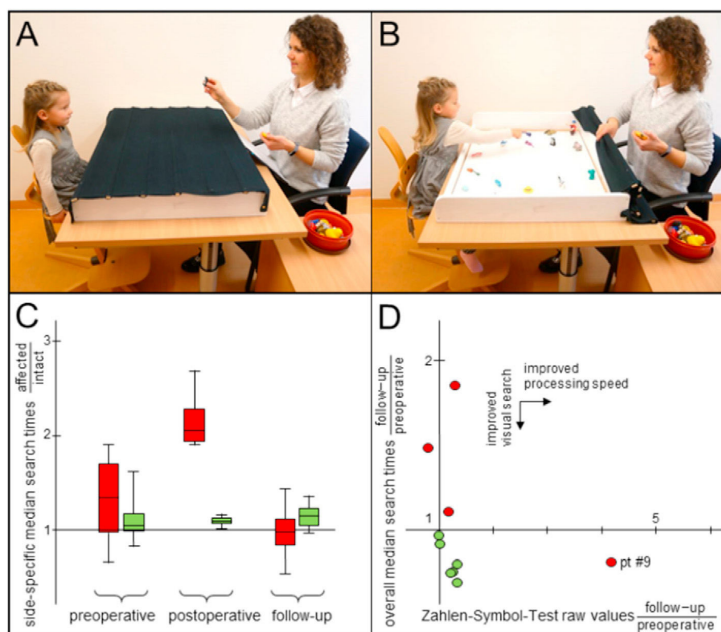
Fig. 1. (A, B) Table Test (modified after Roth et al. [9]). On a white tabletop (60 × 80 cm^2), twenty objects are arranged as two ellipses in a patient's visual angle of 20° and 30°. (A) The patient sits in front of the table, with a predefined distance (37 cm horizontal, 46 cm vertical) between her eye level and the center point of table. A cloth covers the tabletop. At viewing height of the patient, the examiner shows a target object. (B) When the examiner opens the cover, the patient searches the arrangement of objects and, when found, points at the identical object. The examiner measures the search time with a manual stopwatch, covers the objects again, and presents the next object. In this sequence, all twenty objects are presented in a pre-defined order.
(C) Ratios (affected/intact hemifield) of side-specific median search times for the ten objects on each half of the Table Test. Boxplots of patients with newly acquired homonymous hemianopia are displayed in red, of patients with postoperatively intact visual fields in green.
(D) Ratios (follow-up/preoperative) of Zahlen-Symbol-Test raw values and overall median search times in patients with newly acquired hemianopia (in red) and in patients with postoperatively intact visual fields (in green). No Zahlen-Symbol-Test data were available in #8 and #12 due to young age. The findings in patient #9 are explained in ▶Fig. 2.

Regarding visual search, we found that, immediately after the surgery, the patients with newly acquired hemianopias had developed a relative disadvantage for objects in their newly blind hemifield, whereas no asymmetries had developed in controls (▶Fig. 1C) (p < .001; Two-Way Mixed ANOVA with repeated measures). Already six months later, however, this relative disadvantage in the study group had disappeared (p = .36).

Analyzing overall median search times (i.e. comprising both visual half-fields), we found that the five patients who had newly acquired hemianopias showed significantly longer median search times than the seven patients who had undergone surgeries leaving the visual fields intact (F(1, 7) = 13.992, p = .007). Interestingly, this was the case already prior to the surgeries − although, at that time, both subgroups still had intact visual fields, as documented by campimetry. Comparing overall visual search times before and six months after the surgeries, we found that all patients with newly acquired hemianopias had deteriorated (except patient #9), whereas all patients with intact visual fields had improved (except patient #12, not included in Fig. 1D since no Zahlen-Symbol-Test was performed, see above) (▶Fig. 1D).

Regarding processing speed, we found, as expected, a strong negative correlation between the Zahlen-Symbol-Test raw values and the Table Test median search times in the preoperative situation (i.e. with intact visual fields in all patients; r(10) = −0.842; p = .002; Spearman), indicating faster visual search in patients with higher processing speed. Six months after the surgery, processing

speed has improved in all patients except patient #6 (mean = +6 value points) (▶Fig. 1D).

To investigate the differential effects of hemianopia (yes/no) and changes in Zahlen-Symbol-Test raw values ($\frac{follow-up}{preoperative}$) on Table Test median search times ($\frac{follow-up}{preoperative}$), we conducted a stepwise linear multiple regression analysis. The factor hemianopia (beta = 0.689, t = 2.688, p = .028) and the factor Zahlen-Symbol-Test changes (beta = −0.542, t = −2.574, p = .037) were retained in the model as statistically significant predictors, with hemianopia explaining 47.5% of the variance and the Zahlen-Symbol-Test explaining additional 25.5% of changes in Table Test median search times.

4. Discussion

As expected, immediately after acquiring hemianopia, visual search for objects in the newly blind hemifield was markedly impaired compared with objects in the intact hemifield. The major and surprising finding of our study was that, already six months later, all patients had recovered completely regarding this relative side-disadvantage, indicating highly effective mechanisms of compensation. In how far the early compensation found in the present study was influenced by our rehabilitative measures (see ▶Table 1) must be investigated in future studies.

These findings are compatible with studies on adults recording eye movements in hemianopic patients to analyze scanning
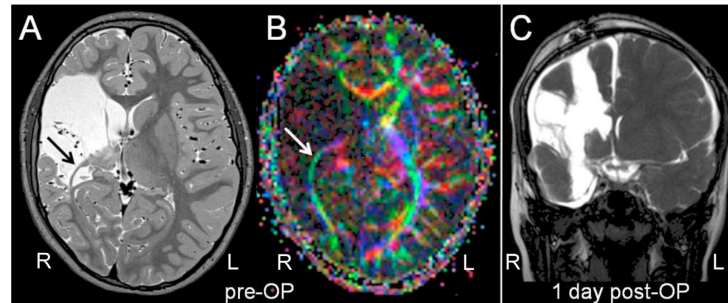
Fig. 2. MRI of patient #9 with improved visual search despite newly acquired hemianopia (see ►Fig. 1D and ►Table 1). This girl suffered from neonatal seizures and developed unilateral spastic cerebral palsy. MRI displayed a (presumably perinatal) infarct in the territory of the right middle cerebral artery leaving the optic radiation intact (A: axial T2-weighted image; B: color-coded fractional anisotropy map; arrows = intact optic radiation). Epilepsy developed at the age of 5 years and never responded sufficiently to anti-epileptic drugs, so that, at the age of 9 years, vertical parasagittal hemispherotomy was performed (C: coronal T2 trufi image). Six months after the surgery, the girl was not only seizure-free, but her concentration and attention span had noticeably improved, her verbal intelligence quotient (IQ) was unchanged at 71, whereas her performance IQ had slightly improved from 54 to 61. Here, the Zahlen-Symbol-Test raw value had improved from 8 (preoperative) to 25 (follow-up). Despite her newly acquired hemianopia, the overall median Table Test search time had improved from 2.0 s (preoperative) to 1.6 s (after 6 months). We hypothesize that the marked improvement in processing speed led to overcompensation for the visual field loss and resulted in net improvement of overall visual search performance. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

patterns [2,4,9–11]. Here, hemianopic patients initially displayed less systematic scan patterns and prolongation of scanpaths [2,4,10]. In the hemianopic direction, patients presented a "staircase strategy" consisting of hypometric, stepwise saccades [10]. Fixations appeared more frequently and were more widely distributed, with a greater proportion of time spent in the blind hemifield [2,4,9,10]. With increasing duration of hemianopia, some patients developed more and more beneficial eye movement strategies such as involuntary exploratory saccades towards the blind hemifield. Searching saccades increased in length and/or overshot the target [2,10,11].

Only few studies exist on visual search in children with hemianopia [3,8]. Tinelli et al. found that patients with congenital visual field defects did not show differences in visual search between both visual field halves, whereas in children with acquired hemianopia (examined at least 11 months after its onset), visual search times were significantly longer when the target was presented in the hemianopic field compared with the intact field [3]. This is in contradiction with our study showing full compensation of the relative disadvantage in the blind hemifield six months after acquiring hemianopia. We can only speculate on the reasons for this discrepancy; potentially relevant differences are the less artificial character of the examinations (e.g. not restricting head movements) and the less challenging task in our study — or the fact that all patients in our cohort received individualized neurorehabilitative measures with special respect to their new hemianopia. Indeed, the computerized saccade training program we used has been shown to improve search times in children. In this study [8], differences between the two hemifields were not assessed. Interestingly, these authors reported that overall search times decreased with increasing age of the children [8]. This could be compatible with our finding of search times correlating with processing speed if one assumes faster processing speed with increasing age in children [12].

Six months after the surgery causing hemianopia, despite a full compensation of the relative disadvantage of objects in the newly blind hemifield, we still found a prolongation of overall visual search times in most hemianopic patients compared with the preoperative assessment. In addition to hemianopia, we identified changes in processing speed as a significant predictor for overall visual search performance, with significant overlapping effects of (a) deterioration by hemianopia and (b) amelioration by improved processing speed (an effect of successful epilepsy surgery).

Interestingly, the five patients who lost one visual hemifield due to epilepsy surgery had shown higher median search times than the control group already preoperatively, i.e., with still intact visual fields. This could indicate that the underlying brain damage and/or the epileptic dysfunction in these children was more severe, justifying the surgical decision to sacrifice one visual hemifield in order to cure the epilepsies.

Admittedly, this study has several limitations. First, the cohort in the study seems quite small; on the other hand, the situation of sacrificing one visual hemifield in children with intact visual fields during epilepsy surgery is rare, so that five patients nevertheless represent a comparatively large sample, allowing statistical group analysis. Second, as patients were not able to be deprived of post-surgery rehabilitative treatment, the study did not include a "control group" of patients that had such surgeries but did not receive any visual therapy. Hence, we could not differentiate between spontaneous compensation and therapy-induced improvement. Third, the children's improvement in Zahlen-Symbol-Test performance postoperatively could possibly have also been influenced by a third variable (other than processing speed), such as better cooperation or focus of attention. In this context, it should be taken into consideration that all five patients with postoperative hemianopia were seizure-free after surgery (Engel 1), while two controls (patient #14 and #15) postoperatively had no worthwile seizure improvement (Engel 4). On the other hand, these two Engel 4 cases showed improvements in both Table Test median search times and Zahlen-Symbol-Test raw values in the follow-up examination compared with the preoperative situation; hence, it seems unlikely that differences in seizure outcome between the two groups influenced our results. Moreover, retest effects could partially explain the improved search times [13]. On the other hand, since retest effects concern both the study group and the control group alike, these effects cannot explain the differences between the two groups. Finally, awareness of the new hemianopia was not assessed in our study. Future studies should investigate whether such awareness could help to compensate, by improving voluntary compensatory mechanisms.

Our study has important clinical implications: Parents of children who will undergo hemianopia-causing surgeries should be informed that effective compensation strategies can be expected to

minimize the disadvantage of the blind hemifield [8]. Nevertheless, side-independent disadvantages in visual search may result, which again might be outweighed by improvement in other cognitive parameters.

Acknowledgements

References

[1] C. Owsley, Visual processing speed, Vis. Res. 90 (2013) 52–56.
[2] J. Zihl, Visual scanning behavior in patients with homonymous hemianopia, Neuropsychologia 33 (3) (1995) 287–303.
[3] F. Tinelli, A. Guzzetta, C. Bertini, D. Ricci, E. Mercuri, E. Ladavas, et al., Greater sparing of visual search abilities in children after congenital rather than acquired focal brain damage, Neurorehabilitation Neural Repair 25 (8) (2011) 721–728.
[4] M.L.M. Tant, F.W. Cornelissen, A.C. Kooijman, W.H. Brouwer, Hemianopic visual field defects elicit hemianopic scanning, Vis. Res. 42 (10) (2002) 1339–1348.
[5] A.L. Pambakian, D.S. Wooding, N. Patel, A.B. Morland, C. Kennard, S.K. Mannan, Scanning the visual world: a study of patients with homonymous hemianopia, J. Neurol. Neurosurg. Psychiatry 69 (6) (2000) 751–759.
[6] Y. Koenraads, D.C.P. van der Linden, M.M.J. van Schooneveld, S.M. Imhof, P.H. Gosselaar, G.L. Porro, et al., Visual function and compensatory mechanisms for hemianopia after hemispherectomy in children, Epilepsia 55 (6) (2014) 909–917.
[7] L. Neumayr, T. Pieper, M. Kudernatsch, S. Trauzettel-Klosinski, M. Staudt, Uncovering homonymous visual field defects in candidates for pediatric epilepsy surgery. Abstracts of the 45th Annual Meeting of the Society for Neuropediatrics, Georg Thieme Verlag KG, 2019.
[8] I.V. Ivanov, S. Kuester, M. MacKeben, A. Krumm, M. Haaga, M. Staudt, et al., Effects of visual search training in children with hemianopia, PloS One 13 (7) (2018), e0197285.
[9] T. Roth, A.N. Sokolov, A. Messias, P. Roth, M. Weller, S. Trauzettel-Klosinski, Comparing explorative saccade and flicker training in hemianopia: a randomized controlled study, Neurology 72 (4) (2009) 324–331.
[10] O. Meienberg, W.H. Zangemeister, M. Rosenberg, W.F. Hoyt, L. Stark, Saccadic eye movement strategies in patients with homonymous hemianopia, Ann. Neurol. 9 (6) (1981) 537–544.
[11] S. Ishiai, T. Furukawa, H. Tsukagoshi, Eye-fixation patterns in homonymous hemianopia and unilateral spatial neglect, Neuropsychologia 25 (4) (1987) 675–679.
[12] R. Kail, Speed of information processing: developmental change and links to intelligence, J. Sch. Psychol. 38 (1) (2000) 51–61.
[13] J. Scharfen, J.M. Peters, H. Holling, Retest effects in cognitive ability tests: a meta-analysis, Intelligence 67 (2018) 44–66.

3   Discussion

3.1   Identification, assessment and prevalence of homonymous visual field defects in pediatric epilepsy surgery patients

3.1.1   Identification of homonymous visual field defects in children

Identification of visual field defects in children presents a major challenge as children often do not complain about visual impairments and, in addition, some patients have excellent compensation strategies so that even experienced examiners do not suspect the presence of visual field defects (Haaga et al. 2018; Harbert et al. 2012; Jacobson et al. 2012; Tinelli et al. 2011). Consideration of special clues in clinical observation, however, can be helpful to prevent homonymous visual field defects in the pediatric population from going unrecognized. Furthermore, neuroimaging techniques are valuable in assessing the integrity of the visual pathway and in prediction of visual field defects. The combination of several methods has great potential to improve our understanding of the visual system and to contribute to the identification of homonymous visual field defects in children.

In Study I, we confirmed strabismus and anomalous head posture as valuable clinical indicators for homonymous visual field defects in an epilepsy surgery setting. We thus claim that clinicians should pay attention to these clinical signs, especially in children with brain lesions (Neumayr et al. 2020b).

Interestingly, most of our patients with strabismus had esotropia. This is in contrast to previous studies, which have suggested exotropia as a compensatory mechanism due to the beneficial lateral extension of the visual field (Donahue and Haun 2007; Jacobson et al. 2012; Koenraads et al. 2014; Koenraads 2016; Levy et al. 1995). The question arises why our study yielded results different from the others. A possible explanation could be provided by comparing strabismus in hemianopic patients with secondary strabismus

caused by eye diseases. While loss of fusion and binocularity due to ocular diseases in adulthood lead to secondary exotropia, the consequence in children is mostly esotropia. It is unclear from which age on the secondary strabismus is more likely exotropia than esotropia (Steffen and Kaufmann 2020). Our patients with visual field defects due to congenital brain lesions were young at onset of strabismus. Therefore, it appears plausible that this was the reason why they tended to present esotropia. We assume that esotropia in our patients is a consequence of insufficient fusion and binocularity due to restricted visual fields and not a compensatory mechanism.

Besides strabismus, a head turn to the non-seeing hemifield is considered a compensatory mechanism in patients with homonymous hemianopia, since the residual visual field is centered (Good et al. 1994). Surprisingly, half of the patients in our study with anomalous head posture showed a head-tilt or a turn towards the seeing hemifield. The reason for this form of anomalous head posture remains unclear.

In our study, strabismus and anomalous head posture had positive predictive values of 86% and 100%, respectively, for the presence of homonymous visual field defects. These unexpectedly high positive predictive values have to be regarded in consideration of the highly selected patient cohort in our study. In an unselected cohort of children, most of the patients with strabismus and / or anomalous head posture do not have visual field defects (Kaufmann and Esser 2012).

3.1.2 Visual field assessment in children

In Study I, we evaluated campimetry for visual field assessment in children. As this test allows uncovering of homonymous visual field defects and is well accepted by most children, including toddlers, we suggest establishment of campimetry in clinical practice (Neumayr et al. 2020b).

Besides campimetry, several methods exist for visual field assessment in children. Even if most of these are relatively unknown and not widely used, they should be taken into account when orthoptists, pediatric neuro-ophthalmologists or pediatric neurologists search for an appropriate testing method.

For various reasons, the type of testing method performed may influence the results. A general distinction is made between kinetic and static perimetry techniques. In kinetic perimetry, a stimulus is moved from a patient's non-seeing area to a seeing area, and the location where the object is first seen is recorded. In static perimetry, in contrast, stationary stimuli are presented with increasing luminance until the threshold of perception is reached. Prior studies have shown that in infants and toddlers, measured visual field extent is larger for moving than for static targets (Delaney et al. 2000; Dobson et al. 1998).

Moreover, test results may depend on whether the execution is automatically computerized or manually performed by an examiner. In automated perimetry, stimulus presentation as well as recording of the patient's responses can be standardized, leading to more reproducible results. Manual perimetry, however, can still be useful, especially in children, since the examiner can aid the patient's performance, keep up motivation and adapt the testing algorithms individually to the patient.

Perimetry methods vary in their demands on the patient's mental and physical skills. Testers should consider how long the patient, particularly children, can sit still and concentrate. Some techniques, especially automated static perimetry, can occupy much more time than, for example, confrontational perimetry or campimetry. In addition, various methods require active verbal or non-verbal responses of the patient, whereas in behavioral methods the patient's eye movements suffice for visual field assessment. As perimetry depends to a great extent on subjective factors such as the patient's cooperation, the examination technique must not exceed the child's capabilities. Though, visual field assessment should be performed to the maximum mental and physical capabilities of the patient. This means that the most sophisticated perimetry

technique possible should be chosen. Therefore, the here presented method of campimetry is well suited for young children and children with cognitive impairments. As a standard campimetry evaluation takes about 10 – 15 minutes, this examination technique is appropriate especially for patients with short attention span. Furthermore, it combines the advantages of static stimuli and manual performance.

When searching for an appropriate testing method, the examiner should also consider the expected type of visual field defect. In patients with retrochiasmal brain lesions, such as some candidates for epilepsy surgery, complete or incomplete homonymous hemianopia can be expected. This visual field defect can be detected by confrontational behavioral methods such as campimetry (Neumayr et al. 2020b). A different type of visual field defect can appear in patients with epilepsy treated with vigabatrin. This anti-epileptic drug can cause visual field constriction, which is detectable by monocular kinetic visual field investigation such as Goldman perimetry (Kedar et al. 2011; Willmore et al. 2009). Due to its 30° radius external examination border, the campimeter is not suitable for identifying vigabatrin-associated peripheral visual field defects (Neumayr et al. 2020b). Furthermore, campimetry is also unable to identify enlarged blind spots, which can appear in children with increased intracranial pressure. These visual field defects can only be detected by automated static perimetry.

In summary, the examiner has to analyze several prerequisites demanded by both the examination method and the patient in order to choose an appropriate testing method for visual field assessment, especially in children. The role of campimetry in this context is that the patient has to meet only low requirements in form of sitting still for 10-15 minutes and following simple instructions.

3.1.3 Prevalence of visual field defects in children with brain diseases

In Study I, we found visual field defects in 56% of pediatric epilepsy surgery patients (Neumayr et al. 2020b). This is in line with prior studies that described

a high prevalence of visual field defects in children with various brain diseases. Porro et al. examined pediatric patients with spastic hemiparesis, detecting visual field defects in as many as 75% of the children (Porro et al. 1999). Other researchers studied children with cerebral palsy and uncovered visual field defects in 56 – 62% (Guzzetta et al. 2001; Jacobson et al. 2010). Mohn et al. assessed visual fields in children with a variety of neurological disorders and found restrictions of the visual field in 64% (Mohn and van Hof-van Duin 1983). Moreover, visual field defects have been reported in 36% of children with hypoxic or ischemic brain injury (Groenendaal et al. 1989; Taylor 1992). All in all, visual field defects are common in children with brain disorders. Therefore, perimetry should be considered routinely in neuropediatric departments, especially when clinical indicators such as strabismus or abnormal head position are present.

3.2   Effects of surgically induced homonymous hemianopia on visual search in pediatric epilepsy surgery patients

In Study II, we analyzed the effects of surgically acquired homonymous hemianopia on visual search times. As expected, we found a relative disadvantage in the newly blind hemifield in the first postoperative days. Surprisingly, this had completely disappeared already after six months. In contrast, overall visual search performance was still impacted after six months. Besides hemianopia, we found changes in processing speed as a significant predictor for median visual search times (Neumayr et al. 2020a).

3.2.1 Visual search patterns in patients with homonymous hemianopia

Several studies have analyzed visual search behavior in hemianopic patients by means of oculography (Meienberg et al.; Meienberg et al. 1981; Pambakian et al. 2000; Tant et al. 2002; Zangemeister et al. 1982; Zihl 1995a; Zihl 1999). This

technique allows the recording of saccades and fixations. A saccade is an eye movement used to redirect the line of vision in order to bring the object of interest onto the fovea (Mezey et al. 1998). A fixation, in contrast, is defined as the maintaining of the gaze on a single location (Komogortsev et al. 2010). Differences in visual search patterns were found between persons with intact visual field and those with homonymous hemianopia (Meienberg et al. 1981; Pambakian et al. 2000; Tant et al. 2002; Zangemeister et al. 1982; Zihl 1995a; Zihl 1999). Subjects with intact visual field use the eccentricity of a new target's image on the retina to calculate the size of a saccade needed to get to it. Thus, when the target is perceived in the peripheral visual field, in most cases a single saccade suffices to reach the target directly. Hemianopic patients, however, do not have visual information about the position of a target in the blind hemifield, rendering visual search more complicated (Meienberg et al. 1981).

Several studies reported that visual search behavior is less systematic in adult patients with homonymous hemianopia than in healthy controls. In hemianopic patients, visual search is characterized by prolongation of scanpaths and search times. During visual search in the direction of the hemianopia, patients present a "staircase strategy" consisting of hypometric, stepwise saccades. Thus, specifically in the blind hemifield, saccades have shorter amplitudes, but occur in higher numbers. Fixations also appear more frequently and are more widely distributed, with a greater proportion of fixation time spent in the blind hemifield (Chédru et al. 1973; Gassel 1963; Ishiai et al. 1987; Kerkhoff 1999; Meienberg et al. 1981; Pambakian et al. 2000; Tant et al. 2002; Zangemeister et al. 1982; Zangemeister 1995; Zihl 1999). In accordance with these findings, Study II showed that in patients with newly-acquired hemianopia, Table Test search times in the blind hemifield increased markedly, indicating disadvantageous visual search patterns in the blind visual field half (Neumayr et al. 2020a).

When a target is repeatedly presented at the same place within the blind hemifield, patients with homonymous hemianopia are capable of learning the target position. Once patients have found the target with the "staircase

strategy", they can increase the length of saccades towards the target, and finally reach it with one large saccade. This ability is called prediction (Meienberg et al.; Meienberg et al. 1981; Meienberg 1983).

With an increasing duration of hemianopia present, some patients develop more and more beneficial eye movement strategies such as involuntary exploratory saccades towards the blind hemifield (Trauzettel-Klosinski 2010). Furthermore, searching saccades can increase in length and can overshoot the target (Meienberg et al. 1981; Meienberg 1983). Zihl has described spontaneous compensation in some patients within three months after onset of homonymous hemianopia (Zihl 1995a; Zihl 1999). In a study of patients with at least six months of preexisting hemianopia, Pambakian observed highly significant evolution of a spontaneous compensatory eye movement strategy (Pambakian et al. 2000). Likewise, Study II confirms these reports on beneficial eye movement strategies occurring after few months of hemianopia present. In our patients, the visual search disadvantage of the blind hemifield compared to the seeing hemifield had disappeared within six months of onset of hemianopia (Neumayr et al. 2020a).

3.2.2 Cognitive abilities underlying visual search

Several cognitive abilities are needed to perform visual search successfully (Hättenschwiler et al. 2019; Treisman and Gelade 1980). In our study patients, we considered these cognitive abilities in measuring processing speed by the Zahlen-Symbol-Test of the Hamburg-Wechsler-Intelligenz Test für Kinder (HAWIK) Version III or the Hamburg-Wechsler-Intelligenz Test für Erwachsene (WIE).

First, visual search involves visual attention, which allows the selection of relevant information while filtering out irrelevant stimuli in the visual field (Desimone and Duncan 1995; McMains and Kastner 2009). Visual attention depends on bottom-up and top-down mechanisms. Bottom-up mechanisms are

considered to operate on raw sensory input and rapidly and involuntarily shifting attention to salient visual features. These mechanisms are referred to as stimulus-driven processes. Top-down mechanisms, conversely, are thought to derive from knowledge about the current task and to be facilitated by the individual's internal valuations or goals, in a user-driven manner (Connor et al. 2004; Wolfe 2010). The anatomical basis of visual attention has been divided into three cognitive networks that carry out the functions of alerting, orienting and executive control (Fan et al. 2005; Fan and Posner 2004; Petersen and Posner 2012; Posner and Petersen 1990). Alerting describes achieving and maintaining a state of high sensitivity to incoming stimuli, whereas orienting represents the ability to prioritize sensory input by selecting a modality or location, and executive control resolves conflict between competing areas of the brain that might be simultaneously active (Carrasco 2011; Ebaid and Crewther 2019; Petersen and Posner 2012; Posner and Petersen 1990; Raz 2004).

Second, visual search requires central processing, which describes the brain's ability to use and interpret visual information. Visual processing comprises the capacity to perceive, analyze, synthesize, and think in visual patterns, including the ability to store and recall visual representations (Hättenschwiler et al. 2019). As visual processing is affected by visual attention, these tasks do not occur independently (Carrasco 2011; Chica and Lupiáñez 2009; Hopfinger and West 2006).

Third, successful visual search performance necessitates working memory. This cognitive system allows individuals to temporarily retain information in an active state and to manipulate and recall this information for a limited period of time after storage (Baddeley 1992; Hättenschwiler et al. 2019).

3.2.3 Visual- versus cognitive-elicited visual search impairments

Considering the cognitive functions underlying visual search, the question arises whether impaired visual search behavior in hemianopic patients is merely

caused by the visual field defect or by additional brain damage. Zihl has suggested that additional lesions to the ipsilateral posterior thalamus or the parieto-occipital cortex results in poor spatial organization of visual scanning (Zihl 1995a). Tant et al., in contrast, have observed impaired visual scanning behavior in healthy subjects without brain damage when hemianopia was simulated. These researchers therefore concluded that oculomotor dysfunctions in patients with homonymous hemianopia do not result from the brain damage but are visually elicited, namely by the visual field defect (Tant et al. 2002). Moreover, visual field defects possibly lead to altered cognitive processing mechanisms. Pambakian et al. have suggested that hemianopic patients trade off "bottom up" processing for a more "top down" cognitive approach in which cognitive mechanisms exert significant control over visual scanning (Pambakian et al. 2000). In our study, we also found evidence for surgical damage to induce additional problems. On the contrary, our patients improved in processing speed. We conclude that both visual and cognitive factors may influence visual search performance in an interaction.

In our study, both hemianopia and changes in visual processing speed were significant predictors for visual search time. Despite the surgically acquired brain damage, all patients except one showed improved processing speed six months after the surgery compared to the preoperative situation (Neumayr et al. 2020a).

3.2.4 Consequences for treatment approaches for homonymous visual field defects

Several rehabilitative strategies have been suggested for homonymous hemianopia in adults. These therapeutic approaches fall into three main groups, namely optical therapies, eye movement-based therapies, and visual field restitution therapies (Lane et al. 2008; Schofield and Leff 2009; Trauzettel-Klosinski 2009, 2012; Trauzettel-Klosinski 2017).

First, optical aids such as prisms can be used in an attempt to improve visual perception by distorting or replacing parts of the intact hemifield with parts of the blind hemifield (Schofield and Leff 2009). This means that the patient's visual field is artificially expanded such that parts of the visual world, which would otherwise fall into the blind field, now appear in the seeing field (Lane et al. 2008). Optical devices may be helpful in a few hemianopic patients, but they are not recommended in general (Bowers et al. 2008; Hedges et al. 1988; Rossetti et al. 1998; Rossi et al. 1990; Schofield and Leff 2009; Trauzettel-Klosinski 2010).

Second, eye movement-based therapies attempt to enlarge the field of gaze by increasing the rate of effective eye movements. These therapies are based on the assumption that the visual field defect itself cannot be changed significantly. Therefore, eye movement-based treatments aim at alleviating disabilities by teaching patients to make frequent eye movements into the blind hemifield and to shift attention to the blind side (Bolognini et al. 2005; Haan et al. 2016; Kerkhoff et al. 1992; Lane et al. 2008; Pambakian et al. 2004; Roth et al. 2009; Schofield and Leff 2009; Trauzettel-Klosinski 2010; Trauzettel-Klosinski 2012; Trauzettel-Klosinski 2017; Zihl 1995b). This treatment approach intends to advantageously harness preexisting eye movement strategies. Thus, understanding visual search patterns, which occur spontaneously in hemianopic patients, is crucial for development of tailored eye movement-based therapies.

Third, visual field restitution therapies are designed to restore visual function in the damaged hemifield. This is both the most ambitious and controversial approach (Lane et al. 2008). Kasten et al. have introduced a computerized visual field restitution treatment method. During a treatment session, the patient fixated on a central point. Simultaneously, visual stimuli were repeatedly presented in the transition zone, which is the border region between the blind and the intact hemifield. Repeated stimulations aimed at activating residual neuronal structures and thus recovering vision in the area of the visual field defect (Kasten et al. 1998). While there was early promise for the potential of such training, subsequent studies have regarded any supposed visual field

increase as the product of undetected eye movements during visual field assessment (Horton 2005; McFadzean 2006; Plant 2005; Reinhard et al. 2005; Roth et al. 2009).

All therapies described were extensively tested in adults. In children, however, research on rehabilitation of homonymous visual field defects is rare. Ivanov et al. have tested visual search training in hemianopic children and have observed improvement in search strategies and in search times (Ivanov et al. 2018). Werth et al. have studied visual field restitution training in children with homonymous hemianopia due to ischemic or traumatic retrogeniculate lesions and have found possible visual field widening (Werth and Moehrenschlager 1999; Werth and Seelos 2005). This effect may trace back to greater neuronal plasticity in children. Therefore, visual field assessment in this study is difficult to interpret and visual field improvements could reflect compensatory mechanisms rather than restorative ones (Lane et al. 2008).

In conclusion, currently rehabilitation strategies are not widely used in homonymous hemianopia, neither in adults nor in children. Compensatory therapies, however, are most promising as several studies have reported significant improvements following the training (Bolognini et al. 2005; Haan et al. 2016; Kerkhoff et al. 1992; Lane et al. 2008; Pambakian et al. 2004; Roth et al. 2009; Schofield and Leff 2009; Trauzettel-Klosinski 2010; Trauzettel-Klosinski 2012; Trauzettel-Klosinski 2017; Zihl 1995b). Further research is required in order to put forward the development of rehabilitation strategies especially for children with homonymous visual field defects. The results of this thesis support approaches of eye movement-based compensation therapy and suggest special visual search training in hemianopic children. This rehabilitation strategy can enhance the patients' spontaneous compensation mechanisms, which were reported in Study II. For successful compensatory training, the children have to fulfil several cognitive requirements. Participants must be able to understand that they have to find specific visual targets, hold the target in working memory, attend to a visual scene, and inhibit attention to distracting stimuli. As compensatory training is a long-term therapy, it requires weeks of

commitment. This can be challenging for young patients, especially when they do not have an appreciation of their own visual impairment (Waddington and Hodgson 2017). Visual search training cannot enlarge the visual field, but it can improve visual search performance in hemianopic children. This therapy has the potential to optimize the patients' visual outcome and to improve their orientation, mobility, independence and quality of life.

4   Summary

Epilepsy surgery is an established treatment option for children with pharmaco-refractory epilepsy. Whenever the resected or disconnected brain area includes parts of the retrochiasmal visual pathway or the visual center, patients suffer homonymous visual field defects postoperatively. Some candidates for pediatric epilepsy surgery have preexisting visual field defects due to the underlying brain damage, meaning that resections of the visual pathway would not produce new visual field defects. Thus, in epilepsy surgery departments, visual field assessment is an important component of presurgical evaluation. In children, however, this examination presents a major challenge due to low cooperation and attention span.

In Study I, we evaluated "campimetry" for visual field testing in children. This examination method was successfully completed in 16/25 patients of an unselected cohort of pediatric epilepsy surgery patients as young as 2 years. We therefore suggest this device for visual field assessment in toddlers as well as in cognitively impaired children. Moreover, we investigated the prevalence of homonymous visual field defects in pediatric epilepsy surgery patients. The prevalence was unexpectedly high in our study cohort (9/16), emphasizing the importance of pursuing this issue. We also analyzed strabismus and anomalous head posture as potential clinical signs for homonymous hemianopia in children. Since both were confirmed as valuable clinical indicators with high positive predictive values (strabismus: 86%; anomalous head posture: 100%), detection of strabismus and / or anomalous head posture in pediatric epilepsy surgery patients requires visual field assessment (Neumayr et al. 2020b).

When epilepsy surgery induces homonymous hemianopia in children, visual search disorders can arise. With an increasing duration of hemianopia, adaptation mechanisms can mitigate impairments. In Study II, we compared visual search behavior in patients with and without surgically acquired hemianopia. In the unique clinical situation of epilepsy surgery in which one

visual hemifield is knowingly sacrificed in the attempt to cure pharmaco-refractory epilepsies we performed a pre / post analysis of the consequences of a newly acquired homonymous hemianopia for visual search. The patients performed an everyday life-like visual search test, called Table Test, few days before and after epilepsy surgery as well as six months postoperatively.

We compared the visual search times of the patients' intact and affected hemifields. Patients showed a marked relative disadvantage of visual search in the newly blind hemifield a few days after epilepsy surgery. Six months later, the children had adapted to this situation, and the relative disadvantage had disappeared completely. Furthermore, we analyzed median search times and their predictability in terms of hemianopia and processing speed. In the six-month follow-up, overall median search times (i.e., combining both hemifields) were still affected in hemianopic children when compared with their preoperative situation. In addition to hemianopia, improved processing speed was a significant predictor for faster median visual search time (Neumayr et al. 2020a). This demonstrates that visual search is influenced by both visual and cognitive abilities, including visual processing. The study results underline that not only seizure freedom, but also achievable cognitive improvements can justify the sacrifice of a visual hemifield in epilepsy surgery.

In order to optimize the outcome of patients with homonymous hemianopia, special rehabilitation is necessary. Our Study II supports the concept of eye movement-based treatment approaches, showing that hemianopic children develop effective compensation strategies to minimize the relative disadvantage of visual search in their blind hemifields. Visual search training might enhance these compensation mechanisms and therefore be beneficial for these young patients.

5 Deutsche Zusammenfassung (German summary)

Epilepsiechirurgie ist eine etablierte Behandlungsoption für Kinder mit pharmakorefraktären Epilepsien. Wenn sich im resezierten oder diskonnektierten Hirnareal Teile der retrochiasmalen Sehbahn oder der Sehrinde befinden, leiden die Patienten postoperativ an homonymen Gesichtsfelddefekten. Ein Teil der Kandidaten für eine pädiatrische epilepsiechirurgische Operation weist vorbestehende Gesichtsfelddefekte aufgrund der zugrunde liegenden epileptogenen Hirnschädigung auf, sodass Resektionen der Sehbahn keine neuen Gesichtsfelddefekte verursachen. In epilepsiechirurgischen Abteilungen ist die Gesichtsfelduntersuchung daher ein wichtiger Bestandteil der präoperativen Diagnostik. Bei Kindern stellt diese Untersuchung aufgrund der reduzierten Kooperation und Aufmerksamkeits-spanne jedoch eine große Herausforderung dar.

In Studie I haben wir die „Kampimetrie" zur Gesichtsfeldtestung bei Kindern evaluiert. Diese Untersuchungsmethode wurde bei 16/25 Patienten einer nicht selektierten Kohorte von pädiatrisch-epilepsiechirurgischen Patienten ab einem Alter von 2 Jahren erfolgreich durchgeführt. Wir empfehlen diese Methode daher zur Gesichtsfeldtestung bei Kleinkindern sowie bei kognitiv beeinträchtigten Kindern. Darüber hinaus untersuchten wir die Prävalenz homonymer Gesichtsfelddefekte bei pädiatrisch-epilepsiechirurgischen Patienten. Die Prävalenz war in unserer Studienkohorte unerwartet hoch (9/16), was die Bedeutung dieses Themas unterstreicht. Außerdem analysierten wir Strabismus und Kopfzwangshaltung als mögliche klinische Hinweise für eine homonyme Hemianopsie bei Kindern. Da beide als wertvolle klinische Indikatoren mit hohen positiv prädiktiven Werten (Strabismus: 86%; Kopfzwangshaltung: 100%) bestätigt wurden, muss die Detektion von Strabismus und / oder Kopfzwangshaltung bei pädiatrisch-epilepsiechirurgischen Patienten eine Gesichtsfeldtestung nach sich ziehen, sofern möglich (Neumayr et al. 2020b).

Wenn eine epilepsiechirurgische Operation bei Kindern eine homonyme Hemianopsie verursacht, können visuelle Suchstörungen auftreten. Mit zunehmender Dauer der Hemianopsie können Anpassungsmechanismen die Beeinträchtigungen mildern. In Studie II haben wir das visuelle Suchverhalten bei Patienten mit und ohne chirurgisch erworbener Hemianopsie verglichen. In der einmaligen klinischen Situation der Epilepsiechirurgie, in welcher eine Gesichtsfeldhälfte wissentlich geopfert wird, um pharmakorefraktäre Epilepsien zu heilen, führten wir eine prä- / post-Analyse der Folgen einer neu erworbenen homonymen Hemianopsie für die visuelle Suche durch. Die Patienten führten wenige Tage vor und nach einer epilepsiechirurgischen Operation sowie sechs Monate postoperativ einen alltagsähnlichen visuellen Suchtest durch, den sogenannten Table-Test.

Wir verglichen die visuellen Suchzeiten in den intakten und betroffenen Gesichtsfeldhälften der Patienten. Wenige Tage nach der epilepsiechirurgischen Operation zeigten die Patienten einen deutlichen relativen Nachteil der visuellen Suche im blind gewordenen Halbfeld. Sechs Monate später hatten sich die Kinder an diese Situation adaptiert und dieser relative Nachteil war vollständig verschwunden. Darüber hinaus analysierten wir die medianen Suchzeiten und ihre Vorhersagbarkeit in Bezug auf Hemianopsie und Verarbeitungsgeschwindigkeit. In der Sechsmonatskontrolle waren die medianen Suchzeiten (d.h. über beide Halbfelder hinweg) bei hemianopen Kindern im Vergleich zu ihrer präoperativen Situation immer noch beeinträchtigt. Neben der Hemianopsie war die Verarbeitungsgeschwindigkeit ein signifikanter Prädiktor für die mediane visuelle Suchzeit (Neumayr et al. 2020a). Dies zeigt, dass die visuelle Suche sowohl von visuellen als auch von kognitiven Fähigkeiten beeinflusst wird, einschließlich der visuellen Verarbeitung. Die Studienergebnisse unterstreichen, dass nicht nur die Anfallsfreiheit, sondern auch erreichbare kognitive Verbesserungen das Opfer einer Gesichtsfeldhälfte bei epilepsiechirurgischen Operationen rechtfertigen können.

Um das Outcome von Patienten mit homonymer Hemianopsie zu optimieren, ist eine spezielle Rehabilitation erforderlich. Unsere Studie II unterstützt das Konzept Augenbewegungs-basierter Behandlungsansätze und zeigt, dass hemianope Kinder wirksame Kompensationsstrategien entwickeln, um den relativen Nachteil der visuellen Suche in ihrem blinden Halbfeld zu minimieren. Visuelles Suchtraining kann möglicherweise diese Kompensations-mechanismen verbessern und daher für diese jungen Patienten von Vorteil sein.

6   References

Allen LE, Slater ME, Proffitt RV, Quarton E, Pelah A (2012) A new perimeter using the preferential looking response to assess peripheral visual fields in young and developmentally delayed children. J AAPOS 16:261–265. https://doi.org/10.1016/j.jaapos.2012.01.006

Anyanwu C, Motamedi GK (2018) Diagnosis and Surgical Treatment of Drug-Resistant Epilepsy. Brain Sci 8. https://doi.org/10.3390/brainsci8040049

Baddeley A (1992) Working memory. Science 255:556–559. https://doi.org/10.1126/science.1736359

Bagolini B (1967) Anomalous correspondence: definition and diagnostic methods. Doc Ophthalmol 23:346–398. https://doi.org/10.1007/bf02550758

Bajer C, Hofer W, Pieper T, Kudernatsch M, Holthausen H, Staudt M (2019) Cognitive Outcome after Hemispherotomy – An Analysis of 75 Children and Adolescents. In: Abstracts of the 45th Annual Meeting of the Society for Neuropediatrics. Georg Thieme Verlag KG

Basheer SN, Connolly MB, Lautzenhiser A, Sherman EMS, Hendson G, Steinbok P (2007) Hemispheric surgery in children with refractory epilepsy: seizure outcome, complications, and adaptive function. Epilepsia 48:133–140. https://doi.org/10.1111/j.1528-1167.2006.00909.x

Basser PJ, Mattiello J, LeBihan D (1994) MR diffusion tensor spectroscopy and imaging. Biophysical Journal 66:259–267. https://doi.org/10.1016/S0006-3495(94)80775-1

Bittar RG, Rosenfeld JV, Klug GL, Hopkins IJ, Harvey AS (2002) Resective surgery in infants and young children with intractable epilepsy. J Clin Neurosci 9:142–146. https://doi.org/10.1054/jocn.2001.0928

Bjørnaes H, Stabell K, Henriksen O, Løyning Y (2001) The effects of refractory epilepsy on intellectual functioning in children and adults. A longitudinal study. Seizure 10:250–259. https://doi.org/10.1053/seiz.2000.0503

Bolognini N, Rasi F, Coccia M, Làdavas E (2005) Visual search improvement in hemianopic patients after audio-visual stimulation. Brain 128:2830–2842. https://doi.org/10.1093/brain/awh656

Bowers AR, Keeney K, Peli E (2008) Community-based trial of a peripheral prism visual field expansion device for hemianopia. Arch Ophthalmol 126:657–664. https://doi.org/10.1001/archopht.126.5.657

Bronstad PM, Peli E, Liu R, Doherty A, Fulton AB (2018) High prevalence of strabismic visual field expansion in pediatric homonymous hemianopia. PLoS ONE 13:e0209213. https://doi.org/10.1371/journal.pone.0209213

Carrasco M (2011) Visual attention: the past 25 years. Vision Res 51:1484–1525. https://doi.org/10.1016/j.visres.2011.04.012

Chédru F, Leblanc M, Lhermitte F (1973) Visual searching in normal and brain-damaged subjects (contribution to the study of unilateral inattention). Cortex 9:94–111

Chica AB, Lupiáñez J (2009) Effects of endogenous and exogenous attention on visual processing: an Inhibition of Return study. Brain Res 1278:75–85. https://doi.org/10.1016/j.brainres.2009.04.011

Chugani HT, Müller RA, Chugani DC (1996) Functional brain reorganization in children. Brain Dev 18:347–356

Ciccarelli O, Toosy AT, Hickman SJ, Parker GJM, Wheeler-Kingshott CAM, Miller DH, Thompson AJ (2005) Optic radiation changes after optic neuritis detected by tractography-based group mapping. Hum Brain Mapp 25:308–316. https://doi.org/10.1002/hbm.20101

Connor CE, Egeth HE, Yantis S (2004) Visual attention: bottom-up versus top-down. Current Biology 14:R850-2. https://doi.org/10.1016/j.cub.2004.09.041

Dalic L, Cook MJ (2016) Managing drug-resistant epilepsy: challenges and solutions. Neuropsychiatr Dis Treat 12:2605–2616. https://doi.org/10.2147/NDT.S84852

Delaney SM, Dobson V, Harvey EM, Mohan KM, Weidenbacher HJ, Leber NR (2000) Stimulus motion increases measured visual field extent in children 3.5 to 30 months of age. Optom Vis Sci 77:82–89. https://doi.org/10.1097/00006324-200002000-00012

Desimone R, Duncan J (1995) Neural mechanisms of selective visual attention. Annu Rev Neurosci 18:193–222. https://doi.org/10.1146/annurev.ne.18.030195.001205

Devlin AM (2003) Clinical outcomes of hemispherectomy for epilepsy in childhood and adolescence. Brain 126:556–566. https://doi.org/10.1093/brain/awg052

Dobson V, Brown AM, Harvey EM, Narter DB (1998) Visual field extent in children 3.5-30 months of age tested with a double-arc LED perimeter. Vision Res 38:2743–2760

Donahue SP, Haun AK (2007) Exotropia and face turn in children with homonymous hemianopia. J Neuroophthalmol 27:304–307. https://doi.org/10.1097/WNO.0b013e31815b9c2a

Duchowny M, Jayakar P, Resnick T, Harvey AS, Alvarez L, Dean P, Gilman J, Yaylali I, Morrison G, Prats A, Altman N, Birchansky S, Bruce J (1998) Epilepsy Surgery in the First Three Years of Life. Epilepsia 39:737–743. https://doi.org/10.1111/j.1528-1157.1998.tb01159.x

Dunkley C, Kung J, Scott RC, Nicolaides P, Neville B, Aylett SE, Harkness W, Cross JH (2011) Epilepsy surgery in children under 3 years. Epilepsy Res 93:96–106. https://doi.org/10.1016/j.eplepsyres.2010.11.002

Ebaid D, Crewther SG (2019) Visual Information Processing in Young and Older Adults. Front Aging Neurosci 11:116. https://doi.org/10.3389/fnagi.2019.00116

Engel J (2011) Another good reason to consider surgical treatment for epilepsy more often and sooner. Arch Neurol 68:707–708. https://doi.org/10.1001/archneurol.2011.113

Fan J, Posner M (2004) Human attentional networks. Psychiatr Prax 31 Suppl 2:S210-4. https://doi.org/10.1055/s-2004-828484

Fan J, McCandliss BD, Fossella J, Flombaum JI, Posner MI (2005) The activation of attentional networks. Neuroimage 26:471–479. https://doi.org/10.1016/j.neuroimage.2005.02.004

Felleman DJ, van Essen DC (1991) Distributed hierarchical processing in the primate cerebral cortex. Cereb Cortex 1:1–47. https://doi.org/10.1093/cercor/1.1.1

Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, Engel J, Forsgren L, French JA, Glynn M, Hesdorffer DC, Lee BI, Mathern GW, Moshé SL, Perucca E, Scheffer IE, Tomson T, Watanabe M, Wiebe S (2014) ILAE official report: a practical clinical definition of epilepsy. Epilepsia 55:475–482. https://doi.org/10.1111/epi.12550

Forsgren L, Beghi E, Oun A, Sillanpää M (2005) The epidemiology of epilepsy in Europe - a systematic review. Eur J Neurol 12:245–253. https://doi.org/10.1111/j.1468-1331.2004.00992.x

Freitag H, Tuxhorn I (2005) Cognitive function in preschool children after epilepsy surgery: rationale for early intervention. Epilepsia 46:561–567. https://doi.org/10.1111/j.0013-9580.2005.03504.x

Gamio S, Melek N (2003) When the patient says no. Management of exotropia with hemianopic visual field defects. Binocul Vis Strabismus Q 18:167–170

Gassel MM (1963) VISUAL FUNCTION IN PATIENTS WITH HOMONYMOUS HEMIANOPIA PART II OCULOMOTOR MECHANISMS. Brain 86:1–36

Gleissner U, Sassen R, Schramm J, Elger CE, Helmstaedter C (2005) Greater functional recovery after temporal lobe epilepsy surgery in children. Brain 128:2822–2829. https://doi.org/10.1093/brain/awh597

Good WV, Jan JE, DeSa L, Barkovich AJ, Groenveld M, Hoyt CS (1994) Cortical visual impairment in children. Survey of Ophthalmology 38:351–364

Goodale MA, Milner AD (1992) Separate visual pathways for perception and action. Trends in Neurosciences 15:20–25. https://doi.org/10.1016/0166-2236(92)90344-8

Groenendaal F, van Hof-van Duin J, Baerts W, Fetter WPF (1989) Effects of perinatal hypoxia on visual development during the first year of (corrected) age. Early Human Development 20:267–279. https://doi.org/10.1016/0378-3782(89)90012-1

Guzzetta A, Fazzi B, Mercuri E, Bertuccelli B, Canapicchi R, van Hof-van Duin J, Cioni G (2001) Visual function in children with hemiplegia in the first years of life. Developmental Medicine & Child Neurology 43:321–329. https://doi.org/10.1017/s0012162201000603

Haaga M, Trauzettel-Klosinski S, Krumm A, Küster S, Ivanov I, Cordey A, Gehrlich C, Staudt M (2018) Homonymous Hemianopia in Children and Adolescents: An MRI Study. Neuropediatrics 49:142–149. https://doi.org/10.1055/s-0037-1618569

Haan GA de, Melis-Dankers BJM, Brouwer WH, Tucha O, Heutink J (2016) The Effects of Compensatory Scanning Training on Mobility in Patients with Homonymous Visual Field Defects: Further Support, Predictive Variables and Follow-Up. PLoS ONE 11:e0166310. https://doi.org/10.1371/journal.pone.0166310

Handley SE, Vargha-Khadem F, Bowman RJ, Liasis A (2017) Visual Function 20 Years After Childhood Hemispherectomy for Intractable Epilepsy. Am J Ophthalmol 177:81–89. https://doi.org/10.1016/j.ajo.2017.02.014

Harbert MJ, Yeh-Nayre LA, O'Halloran HS, Levy ML, Crawford JR (2012) Unrecognized visual field deficits in children with primary central nervous system brain tumors. J Neurooncol 107:545–549. https://doi.org/10.1007/s11060-011-0774-3

Harding GFA, Spencer EL, Wild JM, Conway M, Bohn RL (2002) Field-specific visual-evoked potentials: identifying field defects in vigabatrin-treated children. Neurology 58:1261–1265

Hättenschwiler N, Merks S, Sterchi Y, Schwaninger A (2019) Traditional Visual Search vs. X-Ray Image Inspection in Students and Professionals: Are the Same Visual-Cognitive Abilities Needed? Front Psychol 10:525. https://doi.org/10.3389/fpsyg.2019.00525

Hedges TR, Stunkard J, Twer A (1988) Fresnel-Prismen--ihr Stellenwert in der Rehabilitation homonymer Hemianopsien (Fresnel prisms--their value in the rehabilitation of homonymous hemianopsias). Klin Monbl Augenheilkd 192:568–571. https://doi.org/10.1055/s-2008-1050180

Hermans AJ, van Hof-van Duin J, Oudesluys-Murphy AM (1994) Visual outcome of low-birth-weight infants (1500-2500 g) at one year of corrected age. Acta Paediatr 83:402–407

Herzau V, Bleher I, Joos-Kratsch E (1988) Infantile exotropia with homonymous hemianopia: a rare contraindication for strabismus surgery. Graefes Arch Clin Exp Ophthalmol 226:148–149

Hoffmann MB, Dumoulin SO (2015) Congenital visual pathway abnormalities: a window onto cortical stability and plasticity. Trends in Neurosciences 38:55–65. https://doi.org/10.1016/j.tins.2014.09.005

Hopfinger JB, West VM (2006) Interactions between endogenous and exogenous attention on cortical visual processing. Neuroimage 31:774–789. https://doi.org/10.1016/j.neuroimage.2005.12.049

Horton JC (2005) Vision restoration therapy: confounded by eye movements. British Journal of Ophthalmology 89:792–794. https://doi.org/10.1136/bjo.2005.072967

Horton JC, Fahle M, Mulder T, Trauzettel-Klosinski S (2017) Adaptation, perceptual learning, and plasticity of brain functions. Graefes Arch Clin Exp Ophthalmol 255:435–447. https://doi.org/10.1007/s00417-016-3580-y

Ishiai S, Furukawa T, Tsukagoshi H (1987) Eye-fixation patterns in homonymous hemianopia and unilateral spatial neglect. Neuropsychologia 25:675–679

Ivanov IV, Kuester S, MacKeben M, Krumm A, Haaga M, Staudt M, Cordey A, Gehrlich C, Martus P, Trauzettel-Klosinski S (2018) Effects of visual search training in children with hemianopia. PLoS ONE 13:e0197285. https://doi.org/10.1371/journal.pone.0197285

Jacobson L, Rydberg A, Eliasson A-C, Kits A, Flodmark O (2010) Visual field function in school-aged children with spastic unilateral cerebral palsy related to different patterns of brain damage. Dev Med Child Neurol 52:e184-7. https://doi.org/10.1111/j.1469-8749.2010.03650.x

Jacobson L, Lennartsson F, Pansell T, Oqvist Seimyr G, Martin L (2012) Mechanisms compensating for visual field restriction in adolescents with damage to the retro-geniculate visual system. Eye (Lond) 26:1437–1445. https://doi.org/10.1038/eye.2012.190

Jonas R, Nguyen S, Hu B, Asarnow RF, LoPresti C, Curtiss S, Bode S de, Yudovin S, Shields WD, Vinters HV, Mathern GW (2004) Cerebral hemispherectomy: hospital course, seizure, developmental, language, and motor outcomes. Neurology 62:1712–1721. https://doi.org/10.1212/01.wnl.0000127109.14569.c3

Jonas R, Asarnow RF, LoPresti C, Yudovin S, Koh S, Wu JY, Sankar R, Shields WD, Vinters HV, Mathern GW (2005) Surgery for symptomatic infant-onset epileptic encephalopathy with and without infantile spasms. Neurology 64:746–750. https://doi.org/10.1212/01.WNL.0000151970.29205.70

Joukal M (2017) Anatomy of the Human Visual Pathway. In: Skorkovská K (ed) Homonymous Visual Field Defects, vol 433. Springer International Publishing, Cham, pp 1–16

Kail R (2000) Speed of Information Processing: Developmental Change and Links to Intelligence. Journal of School Psychology 38:51–61. https://doi.org/10.1016/S0022-4405(99)00036-9

Kandel ER, Schwartz JH, Jessell TM (eds) (2000) Principles of neural science, 4. ed. McGraw-Hill Health Professions Division, New York, NY

Kasten E, Wüst S, Behrens-Baumann W, Sabel BA (1998) Computer-based training for the treatment of partial blindness. Nat Med 4:1083–1087. https://doi.org/10.1038/2079

Kaufmann HJ, Esser J (2012) Strabismus, 4., vollständig überarb. und erw. Aufl. Thieme, Stuttgart

Kedar S, Ghate D, Corbett JJ (2011) Visual fields in neuro-ophthalmology. Indian J Ophthalmol 59:103–109. https://doi.org/10.4103/0301-4738.77013

Kerkhoff G (1999) Restorative and compensatory therapy approaches in cerebral blindness - a review. Restor Neurol Neurosci 15:255–271

Kerkhoff G, Münßinger U, Haaf E, Eberle-Strauss G, Stögerer E (1992) Rehabilitation of homonymous scotomata in patients with postgeniculate damage of the visual system: saccadic compensation training. Restor Neurol Neurosci 4:245–254. https://doi.org/10.3233/RNN-1992-4402

Kim Y-J, Yukawa E, Kawasaki K, Nakase H, Sakaki T (2006) Use of multifocal visual evoked potential tests in the objective evaluation of the visual field in pediatric epilepsy surgery. J Neurosurg 104:160–165. https://doi.org/10.3171/ped.2006.104.3.160

Kim J-S, Park E-K, Shim K-W, Kim DS (2018) Hemispherotomy and Functional Hemispherectomy: Indications and Outcomes. J Epilepsy Res 8:1–5. https://doi.org/10.14581/jer.18001

Klistorner AI, Graham SL, Grigg J, Balachandran C (2005) Objective perimetry using the multifocal visual evoked potential in central visual pathway lesions. Br J Ophthalmol 89:739–744. https://doi.org/10.1136/bjo.2004.053223

Koenraads Y, van der Linden DCP, van Schooneveld MMJ, Imhof SM, Gosselaar PH, Porro GL, Braun KPJ (2014) Visual function and compensatory mechanisms for hemianopia after hemispherectomy in children. Epilepsia 55:909–917. https://doi.org/10.1111/epi.12615

Koenraads Y, Braun KPJ, van der Linden DCP, Imhof SM, Porro GL (2015) Perimetry in young and neurologically impaired children: the Behavioral Visual Field (BEFIE) Screening Test revisited. JAMA Ophthalmol 133:319–325. https://doi.org/10.1001/jamaophthalmol.2014.5257

Koenraads Y (2016) Visual field examination in children with brain disorders. https://dspace.library.uu.nl/bitstream/1874/333970/1/Koenraads.pdf

Kolb B, Whishaw IQ (2009) Fundamentals of human neuropsychology, 6th ed. Worth Pub, New York

Komogortsev OV, Gobert DV, Jayarathna S, Koh D-H, Gowda S (2010) Standardization of automated analyses of oculomotor fixation and saccadic behaviors. IEEE Trans Biomed Eng 57. https://doi.org/10.1109/TBME.2010.2057429

Kwan P (2000) P-Glycoprotein and multidrug resistance (MDR) gene expression in epilepsy. Epilepsia 41:161

Kwan P, Brodie MJ (2002) Refractory epilepsy: a progressive, intractable but preventable condition? Seizure 11:77–84. https://doi.org/10.1053/seiz.2002.0593

Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, Moshé SL, Perucca E, Wiebe S, French J (2010) Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 51:1069–1077. https://doi.org/10.1111/j.1528-1167.2009.02397.x

Lane AR, Smith DT, Schenk T (2008) Clinical treatment options for patients with homonymous visual field defects. Clin Ophthalmol 2:93–102. https://doi.org/10.2147/opth.s2371

Laxer KD, Trinka E, Hirsch LJ, Cendes F, Langfitt J, Delanty N, Resnick T, Benbadis SR (2014) The consequences of refractory epilepsy and its treatment. Epilepsy Behav 37:59–70. https://doi.org/10.1016/j.yebeh.2014.05.031

Lee S-K, Kim DI, Kim J, Kim DJ, Kim HD, Kim DS, Mori S (2005) Diffusion-tensor MR imaging and fiber tractography: a new method of describing aberrant fiber connections in developmental CNS anomalies. Radiographics 25:53-65; discussion 66-8. https://doi.org/10.1148/rg.251045085

Leff A (2004) A historical review of the representation of the visual field in primary visual cortex with special reference to the neural mechanisms underlying macular sparing. Brain and Language 88:268–278. https://doi.org/10.1016/S0093-934X(03)00161-5

Levy Y, Turetz J, Krakowski D, Hartmann B, Nemet P (1995) Development of compensating exotropia with anomalous retinal correspondence after early infancy in congenital homonymous hemianopia. J Pediatr Ophthalmol Strabismus 32:236–238

Loddenkemper T, Holland KD, Stanford LD, Kotagal P, Bingaman W, Wyllie E (2007) Developmental outcome after epilepsy surgery in infancy. Pediatrics 119:930–935. https://doi.org/10.1542/peds.2006-2530

Lovie-Kitchin JE, Soong GP, Hassan SE, Woods RL (2010) Visual field size criteria for mobility rehabilitation referral. Optom Vis Sci 87:E948-57. https://doi.org/10.1097/OPX.0b013e3181ff99be

Mayer DL, Fulton AB, Cummings MF (1988) Visual fields of infants assessed with a new perimetric technique. Invest Ophthalmol Vis Sci 29:452–459

McFadzean RM, Condon BC, Barr DB (1999) Functional magnetic resonance imaging in the visual system. J Neuroophthalmol 19:186–200

McFadzean RM (2006) NovaVision: vision restoration therapy. Curr Opin Ophthalmol 17:498–503. https://doi.org/10.1097/ICU.0b013e3280108544

McMains SA, Kastner S (2009) Visual Attention. In: Binder MD, Hirokawa N, Windhorst U (eds) Encyclopedia of neuroscience. Springer, Berlin, Heidelberg, pp 4296–4302

Meienberg O (1983) Clinical examination of saccadic eye movements in hemianopia. Neurology 33:1311–1315

Meienberg O, Harrer M, Wehren C Oculographic diagnosis of hemineglect in patients with homonymous hemianopia. J Neurol 233:97–101. https://doi.org/10.1007/BF00313854

Meienberg O, Zangemeister WH, Rosenberg M, Hoyt WF, Stark L (1981) Saccadic eye movement strategies in patients with homonymous hemianopia. Ann Neurol 9:537–544. https://doi.org/10.1002/ana.410090605

Mezey LE, Harris CM, Shawkat FS, Timms C, Kriss A, West P, Taylor DS (1998) Saccadic strategies in children with hemianopia. Dev Med Child Neurol 40:626–630. https://doi.org/10.1111/j.1469-8749.1998.tb15429.x

Miranda MA, Henson DB, Fenerty C, Biswas S, Aslam T (2016) Development of a Pediatric Visual Field Test. Transl Vis Sci Technol 5. https://doi.org/10.1167/tvst.5.6.13

Mohn G, van Hof-van Duin J (1983) Behavioural and electrophysiological measures of visual functions in children with neurological disorders. Behav Brain Res 10:177–187. https://doi.org/10.1016/0166-4328(83)90163-8

Moosa ANV, Jehi L, Marashly A, Cosmo G, Lachhwani D, Wyllie E, Kotagal P, Bingaman W, Gupta A (2013) Long-term functional outcomes and their predictors after hemispherectomy in 115 children. Epilepsia 54:1771–1779. https://doi.org/10.1111/epi.12342

Moraes CG de (2013) Anatomy of the visual pathways. J Glaucoma 22 Suppl 5:S2-7. https://doi.org/10.1097/IJG.0b013e3182934978

Murray I, Perperidis A, Brash H, Cameron L, McTrusty A, Fleck B, Minns R (2013) Saccadic Vector Optokinetic Perimetry (SVOP): a novel technique for automated static perimetry in children using eye tracking. Conf Proc IEEE Eng Med Biol Soc 2013:3186–3189. https://doi.org/10.1109/EMBC.2013.6610218

Murray IC, Fleck BW, Brash HM, Macrae ME, Tan LL, Minns RA (2009) Feasibility of saccadic vector optokinetic perimetry: a method of automated static perimetry for children using eye tracking. Ophthalmology 116:2017–2026. https://doi.org/10.1016/j.ophtha.2009.03.015

Murray IC, Cameron LA, McTrusty AD, Perperidis A, Brash HM, Fleck BW, Minns RA (2016) Feasibility, Accuracy, and Repeatability of Suprathreshold Saccadic Vector Optokinetic Perimetry. Transl Vis Sci Technol 5:15. https://doi.org/10.1167/tvst.5.4.15

Neumayr L, Gschaidmeier A, Trauzettel-Klosinski S, Pieper T, Kudernatsch M, Hofer W, Bajer C, Staudt M (2020a) Sacrificing one visual hemifield during pediatric epilepsy surgery: Effects on visual search. Eur J Paediatr Neurol 29:103–107. https://doi.org/10.1016/j.ejpn.2020.09.003

Neumayr L, Pieper T, Kudernatsch M, Trauzettel-Klosinski S, Staudt M (2020b) Uncovering homonymous visual field defects in candidates for pediatric epilepsy surgery. Eur J Paediatr Neurol 25:165–171. https://doi.org/10.1016/j.ejpn.2019.11.003

O'Donnell LJ, Westin C-F (2011) An introduction to diffusion tensor image analysis. Neurosurg Clin N Am 22:185-96, viii. https://doi.org/10.1016/j.nec.2010.12.004

Okada T, Miki Y, Kikuta K, Mikuni N, Urayama S, Fushimi Y, Yamamoto A, Mori N, Fukuyama H, Hashimoto N, Togashi K (2007) Diffusion tensor fiber tractography for arteriovenous malformations: quantitative analyses to evaluate the corticospinal tract and optic radiation. AJNR Am J Neuroradiol 28:1107–1113. https://doi.org/10.3174/ajnr.A0493

Owsley C (2013) Visual processing speed. Vision Res 90:52–56. https://doi.org/10.1016/j.visres.2012.11.014

Palace J, Lang B (2000) Epilepsy: an autoimmune disease? J Neurol Neurosurg Psychiatry 69:711–714. https://doi.org/10.1136/jnnp.69.6.711

Palma L de, Pietrafusa N, Gozzo F, Barba C, Carfi-Pavia G, Cossu M, Benedictis A de, Genitori L, Giordano F, Lo Russo G, Marras CE, Pelliccia V, Rizzi S, Rossi-Espagnet C, Vigevano F, Guerrini R, Tassi L, Specchio N (2019) Outcome after hemispherotomy in patients with intractable epilepsy: Comparison of techniques in the Italian experience. Epilepsy Behav 93:22–28. https://doi.org/10.1016/j.yebeh.2019.01.006

Pambakian AL, Wooding DS, Patel N, Morland AB, Kennard C, Mannan SK (2000) Scanning the visual world: a study of patients with homonymous hemianopia. J Neurol Neurosurg Psychiatry 69:751–759

Pambakian ALM, Mannan SK, Hodgson TL, Kennard C (2004) Saccadic visual search training: a treatment for patients with homonymous hemianopia. J Neurol Neurosurg Psychiatry 75:1443–1448. https://doi.org/10.1136/jnnp.2003.025957

Panigrahi M, Krishnan SS, Vooturi S, Vadapalli R, Somayajula S, Jayalakshmi S (2016) An observational study on outcome of hemispherotomy in children with refractory epilepsy. Int J Surg 36:477–482. https://doi.org/10.1016/j.ijsu.2015.05.049

Paysse EA, Coats DK (1997) Anomalous head posture with early-onset homonymous hemianopia. J AAPOS 1:209–213

Pel JJM, van Beijsterveld MCM, Thepass G, van der Steen J (2013) Validity and Repeatability of Saccadic Response Times Across the Visual Field in Eye Movement Perimetry. Transl Vis Sci Technol 2:3. https://doi.org/10.1167/tvst.2.7.3

Petersen SE, Posner MI (2012) The attention system of the human brain: 20 years after. Annu Rev Neurosci 35:73–89. https://doi.org/10.1146/annurev-neuro-062111-150525

Pierpaoli C, Jezzard P, Basser PJ, Barnett A, Di Chiro G (1996) Diffusion tensor MR imaging of the human brain. Radiology 201:637–648. https://doi.org/10.1148/radiology.201.3.8939209

Plant GT (2005) A work out for hemianopia. British Journal of Ophthalmology 89:2. https://doi.org/10.1136/bjo.2004.053173

Porro G, van Nieuwenhuizen O, Wittebol-Post D, Schenk-Rootlieb AJF, Treffers WF (1999) Visual functions in congenital hemiplegia. Neuro-Ophthalmology 21:59–68. https://doi.org/10.1076/noph.21.2.59.3913

Porro G, van der Linden D, van Nieuwenhuizen O, Wittebol-Post D (2005) Role of visual dysfunction in postural control in children with cerebral palsy. Neural Plast 12:205-10; discussion 263-72

Posner MI, Petersen SE (1990) The attention system of the human brain. Annu Rev Neurosci 13:25–42. https://doi.org/10.1146/annurev.ne.13.030190.000325

Prasad S, Galetta SL (2011) Anatomy and physiology of the afferent visual system. Handb Clin Neurol 102:3–19. https://doi.org/10.1016/B978-0-444-52903-9.00007-8

Quinn GE, Dobson V, Hardy RJ, Tung B, Phelps DL, Palmer EA (1996) Visual fields measured with double-arc perimetry in eyes with threshold retinopathy of prematurity from the cryotherapy for retinopathy of prematurity trial. The CRYO-Retinopathy of Prematurity Cooperative Group. Ophthalmology 103:1432–1437

Ramantani G, Kadish NE, Strobl K, Brandt A, Stathi A, Mayer H, Schubert-Bast S, Wiegand G, Korinthenberg R, Stephani U, van Velthoven V, Zentner J, Schulze-Bonhage A, Bast T (2013) Seizure and cognitive outcomes of epilepsy surgery in infancy and early childhood. Eur J Paediatr Neurol 17:498–506. https://doi.org/10.1016/j.ejpn.2013.03.009

Raz A (2004) Anatomy of attentional networks. Anat Rec B New Anat 281:21–36. https://doi.org/10.1002/ar.b.20035

Raz N, Levin N (2014) Cortical and white matter mapping in the visual system-more than meets the eye: on the importance of functional imaging to understand visual system pathologies. Front Integr Neurosci 8. https://doi.org/10.3389/fnint.2014.00068

Reinhard J, Schreiber A, Schiefer U, Kasten E, Sabel BA, Kenkel S, Vonthein R, Trauzettel-Klosinski S (2005) Does visual restitution training change absolute homonymous visual

field defects? A fundus controlled study. British Journal of Ophthalmology 89:30–35. https://doi.org/10.1136/bjo.2003.040543

Reinholdson J, Olsson I, Edelvik A, Hallböök T, Lundgren J, Rydenhag B, Malmgren K (2015) Long-term follow-up after epilepsy surgery in infancy and early childhood--a prospective population based observational study. Seizure 30:83–89. https://doi.org/10.1016/j.seizure.2015.05.019

Reith W (2015) Diffusionsgewichtete Bildgebung (Diffusion-weighted imaging). Radiologe 55:760–761. https://doi.org/10.1007/s00117-015-0008-3

Rossetti Y, Rode G, Pisella L, Farné A, Li L, Boisson D, Perenin MT (1998) Prism adaptation to a rightward optical deviation rehabilitates left hemispatial neglect. Nature 395:166–169. https://doi.org/10.1038/25988

Rossi PW, Kheyfets S, Reding MJ (1990) Fresnel prisms improve visual perception in stroke patients with homonymous hemianopia or unilateral visual neglect. Neurology 40:1597–1599. https://doi.org/10.1212/wnl.40.10.1597

Roth T, Sokolov AN, Messias A, Roth P, Weller M, Trauzettel-Klosinski S (2009) Comparing explorative saccade and flicker training in hemianopia: a randomized controlled study. Neurology 72:324–331. https://doi.org/10.1212/01.wnl.0000341276.65721.f2

Roth J, Nagar S, Constantini S, Fried I (2017) HEMISPHEROTOMY FOR TREATMENT OF REFRACTORY EPILEPSY IN CHILDREN. Harefuah 156:482–485

Saleh GM, Sivaprasad S, Hammond CJ (2006) Homonymous hemianopia and exotropia: an important management issue. Eye (Lond) 20:1402–1404. https://doi.org/10.1038/sj.eye.6702258

Satgunam P, Datta S, Chillakala K, Bobbili KR, Joshi D (2017) Pediatric Perimeter-A Novel Device to Measure Visual Fields in Infants and Patients with Special Needs. Transl Vis Sci Technol 6:3. https://doi.org/10.1167/tvst.6.4.3

Scharfen J, Peters JM, Holling H (2018) Retest effects in cognitive ability tests: A meta-analysis. Intelligence 67:44–66. https://doi.org/10.1016/j.intell.2018.01.003

Schinkel AH (1997) The physiological function of drug-transporting P-glycoproteins. Seminars in Cancer Biology 8:161–170. https://doi.org/10.1006/scbi.1997.0068

Schofield TM, Leff AP (2009) Rehabilitation of hemianopia. Curr Opin Neurol 22:36–40. https://doi.org/10.1097/WCO.0b013e32831f1b2c

Schor C (2015) Perceptual-motor computational model of anomalous binocular correspondence. Optom Vis Sci 92:544–550. https://doi.org/10.1097/OPX.0000000000000586

Sheridan MD (1973) The STYCAR graded-balls vision test. Dev Med Child Neurol 15:423–432

Shimizu H (2005) Our experience with pediatric epilepsy surgery focusing on corpus callosotomy and hemispherotomy. Epilepsia 46 Suppl 1:30–31. https://doi.org/10.1111/j.0013-9580.2005.461009.x

Skirrow C, Cross JH, Cormack F, Harkness W, Vargha-Khadem F, Baldeweg T (2011) Long-term intellectual outcome after temporal lobe surgery in childhood. Neurology 76:1330–1337. https://doi.org/10.1212/WNL.0b013e31821527f0

Spencer EL, Harding GFA (2003) Examining visual field defects in the paediatric population exposed to vigabatrin. Doc Ophthalmol 107:281–287

Steffen H, Kaufmann HJ (2020) Strabismus, 5., vollständig überarbeitete Auflage

Steinbok P, Gan PYC, Connolly MB, Carmant L, Barry Sinclair D, Rutka J, Griebel R, Aronyk K, Hader W, Ventureyra E, Atkinson J (2009) Epilepsy surgery in the first 3 years of life: a Canadian survey. Epilepsia 50:1442–1449. https://doi.org/10.1111/j.1528-1167.2008.01992.x

Sugimoto T, Otsubo H, Hwang PA, Hoffman HJ, Jay V, III OCS (1999) Outcome of Epilepsy Surgery in the First Three Years of Life. Epilepsia 40:560–565. https://doi.org/10.1111/j.1528-1157.1999.tb05557.x

Tailor V, Glaze S, Unwin H, Bowman R, Thompson G, Dahlmann-Noor A (2016) Saccadic vector optokinetic perimetry in children with neurodisability or isolated visual pathway lesions: observational cohort study. Br J Ophthalmol 100:1427–1432. https://doi.org/10.1136/bjophthalmol-2015-307208

Tant MLM, Cornelissen FW, Kooijman AC, Brouwer WH (2002) Hemianopic visual field defects elicit hemianopic scanning. Vision Res 42:1339–1348

Taylor J (1992) Visual Evoked Potentials in Infants and Children. Journal of Clinical Neurophysiology 9:357–372

Téllez-Zenteno JF, Dhar R, Wiebe S (2005) Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. Brain 128:1188–1198. https://doi.org/10.1093/brain/awh449

Terpening Z, Watson JDG (2007) CHAPTER 5 - HIGHER VISUOPERCEPTUAL DISORDERS AND DISORDERS OF SPATIAL COGNITION. In: Schapira AHV, Byrne EMD (eds) Neurology and clinical neurosciences. Mosby, Philadelphia, pp 59–71

Tinelli F, Guzzetta A, Bertini C, Ricci D, Mercuri E, Ladavas E, Cioni G (2011) Greater sparing of visual search abilities in children after congenital rather than acquired focal brain damage. Neurorehabil Neural Repair 25:721–728. https://doi.org/10.1177/1545968311407780

Trauzettel-Klosinski S (2009) Rehabilitation bei Sehbahnschäden (Rehabilitation of lesions in the visual pathways). Klin Monatsbl Augenheilkd 226:897–907. https://doi.org/10.1055/s-0028-1109874

Trauzettel-Klosinski S (2010) Rehabilitation for visual disorders. J Neuroophthalmol 30:73–84. https://doi.org/10.1097/WNO.0b013e3181ce7e8f

Trauzettel-Klosinski S (2012) Visuelles Rehabilitationstraining bei homonymen Gesichtsfeldausfällen (Visual rehabilitation training for homonymous field defects). Ophthalmologe 109:496–500. https://doi.org/10.1007/s00347-012-2571-6

Trauzettel-Klosinski S (2017) Adaptation and Rehabilitation in Patients with Homonymous Visual Field Defects. In: Skorkovská K (ed) Homonymous Visual Field Defects. Springer International Publishing, Cham, pp 161–173

Treisman AM, Gelade G (1980) A feature-integration theory of attention. Cogn Psychol 12:97–136

van Hof-van Duin J, Cioni G, Bertuccelli B, Fazzi B, Romano C, Boldrini A (1998) Visual outcome at 5 years of newborn infants at risk of cerebral visual impairment. Dev Med Child Neurol 40:302–309. https://doi.org/10.1111/j.1469-8749.1998.tb15381.x

Viggedal G, Olsson I, Carlsson G, Rydenhag B, Uvebrant P (2013) Intelligence two years after epilepsy surgery in children. Epilepsy Behav 29:565–570. https://doi.org/10.1016/j.yebeh.2013.10.012

Waddington J, Hodgson T (2017) Review of rehabilitation and habilitation strategies for children and young people with homonymous visual field loss caused by cerebral vision impairment. British Journal of Visual Impairment 35:197–210. https://doi.org/10.1177/0264619617706100

Wandell BA, Winawer J (2010) Imaging retinotopic maps in the human brain. Vision Res 51:718–737. https://doi.org/10.1016/j.visres.2010.08.004

Werth R, Moehrenschlager M (1999) The development of visual functions in cerebrally blind children during a systematic visual field training. Restor Neurol Neurosci 15:229–241

Werth R, Seelos K (2005) Restitution of visual functions in cerebrally blind children. Neuropsychologia 43:2011–2023. https://doi.org/10.1016/j.neuropsychologia.2005.03.023

Willmore LJ, Abelson MB, Ben-Menachem E, Pellock JM, Shields WD (2009) Vigabatrin: 2008 update. Epilepsia 50:163–173. https://doi.org/10.1111/j.1528-1167.2008.01988.x

Wolfe JM (2010) Visual search. Current Biology 20:R346-R349. https://doi.org/10.1016/j.cub.2010.02.016

Wu W, Rigolo L, O'Donnell LJ, Norton I, Shriver S, Golby AJ (2012) Visual pathway study using in vivo diffusion tensor imaging tractography to complement classic anatomy. Neurosurgery 70:145-56; discussion 156. https://doi.org/10.1227/NEU.0b013e31822efcae

Wyllie E, Comair YG, Kotagal P, Raja S, Ruggieri P (1996) Epilepsy Surgery in Infants. Epilepsia 37:625–637. https://doi.org/10.1111/j.1528-1157.1996.tb00626.x

Yukawa E, Kim Y-J, Kawasaki K, Taketani F, Hara Y (2005) A child with epilepsy in whom multifocal VEPs facilitated the objective measurement of the visual field. Epilepsia 46:577–579. https://doi.org/10.1111/j.0013-9580.2005.48204.x

Yukawa E, Matsuura T, Kim Y-J, Taketani F, Hara Y (2008) Usefulness of multifocal VEP in a child requiring perimetry. Pediatr Neurol 38:360–362. https://doi.org/10.1016/j.pediatrneurol.2008.01.002

Zangemeister WH (1995) Short-term adaptation of eye movements in patients with visual hemifield defects indicates high level control of human scanpath. Optom Vis Sci 72:467–477

Zangemeister WH, Meienberg O, Stark L, Hoyt WF (1982) Eye-head coordination in homonymous hemianopia. J Neurol 226:243–254

Zihl J (1995a) Visual scanning behavior in patients with homonymous hemianopia. Neuropsychologia 33:287–303. https://doi.org/10.1016/0028-3932(94)00119-A

Zihl J (1995b) Visual scanning behavior in patients with homonymous hemianopia. Neuropsychologia 33:287–303

Zihl J (1999) Oculomotor scanning performance in subjects with homonymous visual field disorders. Visual Impairment Research 1:23–31. https://doi.org/10.1076/vimr.1.1.23.4450

7   Author contributions

7.1   General

This thesis was performed in the Center for Pediatric Neurology, Neurorehabilitation and Epileptology, Schoen Klinik Vogtareuth, under the supervision of Prof. Dr. med. Martin Staudt. I declare that I independently wrote the manuscript and used neither sources other than those indicated, nor any aids other than those permissible. I appropriately declared all citations.

7.2   Concerning the results of "Uncovering homonymous visual field defects in candidates for pediatric epilepsy surgery"

Study conception and design were performed by Prof. Dr. med. Martin Staudt and me. I selected the methods in cooperation with Prof. Dr. med. Martin Staudt and Prof. Dr. med. Susanne Trauzettel-Klosinski. All tests were carried out by me. I analyzed data in cooperation with Prof. Dr. med. Martin Staudt. I interpreted the results and wrote the manuscript in collaboration with Dipl.-Med. Tom Pieper, Dr. med. Manfred Kudernatsch, Prof. Dr. med. Susanne Trauzettel-Klosinski, and Prof. Dr. med. Martin Staudt.

7.3   Concerning the results of "Sacrificing one visual hemifield during pediatric epilepsy surgery: effects on visual search"

Study conception and design were performed by Prof. Dr. med. Martin Staudt and me. I selected the methods in cooperation with Prof. Dr. med. Martin Staudt, Dipl. Psych. Wiebke Hofer and Dipl. Psych. Christina Bajer. I performed the Table Test. Dipl. Psych. Wiebke Hofer and Dipl. Psych. Christina Bajer performed the Zahlen-Symbol-Test as part of their clinical routine. I analyzed data in cooperation with Alisa Gschaidmeier, Prof. Dr. med. Martin Staudt, Dipl. Psych. Wiebke Hofer and Dipl. Psych. Christina Bajer. I interpreted the results

and wrote the manuscript in collaboration with Alisa Gschaidmeier, Prof. Dr. med. Susanne Trauzettel-Klosinski, Dipl.-Med. Tom Pieper, Dr. med. Manfred Kudernatsch, Dipl. Psych. Wiebke Hofer, Dipl. Psych. Christina Bajer and Prof. Dr. med. Martin Staudt.

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