Accepted Manuscript

Visual Function Twenty Years After Childhood Hemispherectomy for Intractable Epilepsy

Sian E. Handley, B.Med Sci, MSc, Faraneh Vargha-Khadem, PhD, Richard J. Bowman, MD, FRCOphth, Alki Liasis, PhD

PII: S0002-9394(17)30074-0

DOI: 10.1016/j.ajo.2017.02.014

Reference: AJOPHT 10050

To appear in: American Journal of Ophthalmology

Received Date: 20 October 2016

Revised Date: 10 February 2017

Accepted Date: 15 February 2017

Please cite this article as: Handley SE, Vargha-Khadem F, Bowman RJ, Liasis A, Visual Function Twenty Years After Childhood Hemispherectomy for Intractable Epilepsy, *American Journal of Ophthalmology* (2017), doi: 10.1016/j.ajo.2017.02.014.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



Abstract:

Purpose: To investigate visual function in adults post hemispherectomy in childhood. **Design:** Non-comparative case series.

Methods: All participants underwent visual acuity, binocular function, visual field, optical coherence tomography (OCT) of the retinal nerve fiber layer (RNFL), and monocular pattern reversal visually evoked potentials (prVEP).

Participants: 6 adults who had a hemispherectomy in childhood (median 21.5 years post-op).

Main Outcome Measures: Comparison was made of visual acuity, visual field height, global RNFL thickness and prVEP amplitude evoked by full and half field stimulation. Comparison of the eye ipsilateral to the side of surgery to the contralateral eye was achieved employing paired t-tests to the visual function measures.

Results: All participants had homonymous hemianopia. The residual seeing visual field was constricted in all cases when compared to normative data despite crossing the midline into the blind hemi field in 11/12 eyes. This observation was supported by prVEP's to stimuli presented in the blind half field. The height of visual field was smaller in the eye contralateral to side of surgery compared to the ipsilateral side (P=0.047). Visual acuity and RNFL thickness also showed greater diminution in the eye contralateral (P=0.040 and P=0.0004). Divergent strabismus was in four participants with greater field loss.

Conclusions: Adults post hemispherectomy in childhood may have better visual function in the eye ipsilateral to the side of the hemispherectomy compared to the contralateral eye. Possible mechanisms of the inter-ocular difference are discussed. Though visual fields and prVEP responses demonstrate evidence of re-organization in to the blind half field, they also reveal significant un-expected constriction of the functional field.

Visual Function Twenty Years After Childhood Hemispherectomy for Intractable Epilepsy

Authors: Sian E Handley, B.Med Sci, MSc,^{1, 2} Faraneh Vargha-Khadem, PhD,³ Richard J Bowman, MD, FRCOphth,^{1,2} Alki Liasis, PhD,^{1, 2}

Corresponding author: Dr Alki Liasis

Address for reprints: Clinical and Academic Department of Ophthalmology, Great Ormond Street Hospital for Children, Great Ormond Street, London, WC1N 3JH. Word count: 3644 (excluding title page, abstract, references figures and legends)

Short title: Visual Function Twenty Years After Childhood Hemispherectomy

Definition of abbreviations:

prVEP pattern reversal visually evoked potential

- **OCT** Optical coherence tomography
- **RNFL** Retinal nerve fiber layer

1) Clinical and Academic Department of Ophthalmology, Great Ormond Street Hospital for Children, London, UK.

2) Institute of Child Health, University College London, London, UK.

3) Cognitive Neuroscience and Neuropsychiatry Section, University College London Institute of Child Health, and Great Ormond Street Hospital, London, UK.

Introduction

A hemispherectomy is a surgical procedure that involves the disconnection and in some cases removal of a dysfunctional hemisphere of the brain from the rest of the nervous system. This surgery is indicated in cases of pharmaco-resistant epilepsy that has a focus in one hemisphere where more conservative neuro-surgery would not be effective. The surgical procedure is very effective, achieving long-term seizure freedom in 73% of cases¹. Despite hemispherectomy being first described over 85 years ago and the surgical technique evolving over time, it is still currently a neurosurgical procedure carried out in well-selected clinical cases. The earliest form of the surgery was the anatomical hemispherectomy comprising of removal of the entire hemisphere. This had a relatively high complication rate due to hydrocephalus and superficial cerebral hemosiderosis². As a result, in 1983 Rasmussen introduced the functional hemispherectomy in which combined partial anatomic excision and disconnection of the remaining hemisphere, which reduced post surgical complications². More recently the procedure has been modified and renamed hemispherotomy which has been associated with a further reduction in complications¹.

As part of a child's pre-surgical assessment for hemisphectomy, visual fields are assessed to predict how much of a change the patient will notice from their inevitable dense post-operative homonymous hemianopia. Kinetic perimetry has been reported to be feasible in some children from 5 years of age³, though some children with severe epilepsy also have developmental delay. In those who cannot accurately perform kinetic visual fields, visual fields to confrontation have been shown to be 78.6% effective in detection of dense homonymous hemianopia in normal adults⁴.

In order to overcome this problem, in many centers visually evoked potentials (VEP) are used in conjunction with visual field assessment to look for asymmetries indicative of a homonymous hemianopia. By using an array of a minimum of three electrodes (over the right occiput, left occiput and midline) the electrophysiologist can detect homonymous asymmetries under monocular conditions which indicate hemisphere dysfunction^{5–8}. This evidence of visual field deficit is particularly useful in children where behavioral visual fields are limited.

Anterograde transynaptic degeneration at the lateral geniculate nucleus gives rise to changes at the peripapillary nerve fiber layer and optic disc, visible with fundoscopy if severe and with optical coherence tomography (OCT) in milder cases. Using fundoscopy and fundus photography, Hoyt studied a group of young adults with congenital cerebral hemiatrophy and corresponding field defects^{9,10}. He described predominant loss of nasal and temporal peripapillary nerve fibers in the contralateral eye (corresponding to the nasal retinal fibers including the papillomacular bundle, which cross at the chiasm) versus predominant loss of superior and inferior peripapillary nerve fibers in the ipsilateral eye (corresponding to temporal retinal fibers, predominantly uncrossed at the chiasm). These relative patterns of sparing and loss of the retinal nerve fiber layer (RNFL) that Hoyt originally described has been measured and further investigated in man using OCT. The pattern of nerve fiber layer distribution is detectable and measurable using OCT in homonymous hemianopia caused by both acquired^{11,12} and congenital¹³ pathology. On ophthalmoscopy, these RNFL changes may be less obvious in acquired homonymous

hemianopias compared to congenital, however a recent OCT study revealed that both have similar degrees of RNFL thinning¹⁴. Therefore OCT has become a useful tool in pre and postoperative evaluation of RNFL thickness.

Whilst post hemispherectomy motor, speech, language, cognitive and behavioral function have been well studied^{15–18}, the long term consequences on visual function are relatively unknown. Work has been done in blind sight and reorganization into the blind field, with many papers demonstrating a strip of functional vision extending into the blind half field of approximately 3 degrees due to re-organization of the retinotopic map as a result of cortical plasticity in childhood^{19–24}. One study has reported ophthalmic findings post hemispherectomy, focusing on the compensatory mechanisms for the hemianopia including anomalous head posture and constant or intermittent exotropia contralateral to the side of hemianopia²⁵. This was shown to have some adaptive benefit in terms of functional visual field. The long-term natural history of such adaptive exotropia, and its amblyogenic potential has not been previously investigated. We aimed to investigate the relationship between ocular alignment and visual fields in the long term.

This study aimed to investigate the longer-term consequences of childhood hemispherectomy on visual function and adaptive mechanisms, including acuity, field, cortical evoked responses and binocularity, into adulthood and investigate any relationship between these functions and changes in the RNFL as measured by OCT.

Methods:

The study was an observational case series with 6 participants (12 eyes) recruited from the neuropsychology department of Great Ormond Street Hospital for Children, London. The study was approved by the National Health Service Research Ethics Committee for London – City Road & Hampstead and followed the tenets of the Declaration of Helsinki. A summary of all participants is shown in table 1. All participants underwent hemispherectomy (5/6 right functional 1/6 left anatomical) in childhood for intractable epilepsy caused by congenital pathology. They had all had good outcomes in language and motor function, and all remained seizure free postoperative. They were tested a median of 21.5 years after surgery (range 6.3 to 28.8 years) at a single visit (Table 1). All participants were intellectually capable of completing all testing accurately. The work was conducted at the Institute of Child Health, University College London, UK.

All participants underwent the following assessments: monocular visual acuity, ocular motility examination, kinetic visual fields, OCT, and pattern reversal (pr) VEP. Any differences in eyes ipsilateral to surgery compared to contralateral were examined employing 2 tailed paired t-tests. Any previous ophthalmic information available was obtained from their medical notes.

Visual acuity and binocular function

Visual acuity was tested monocularly with appropriate refractive correction, down to threshold using a Log MAR chart at 4 meters (ETDRS - Precision Vision, Illinois USA). A normal monocular acuity was considered to be between 0.000 to 0.100 and a significant interocular difference if there was a difference of one line (0.100) or more. All participants had their ocular motility and the presence of any manifest or latent deviation assessed by an orthoptist. The Frisby stereotest (Clement Clarke International, Essex UK) was used to assess stereopsis.

Visual fields

All participants undertook monocular kinetic visual field assessment (Goldmann -Haag Streit, Bern Switzerland) with a background luminance of 31.5 apostilb. Their capability to be a reliable witness was first assessed using visual fields to confrontation, and then with some test points. Each 15 degree meridian was tested in a random order. Testing was first conducted using the labs standard stimulus (I4e) though this had to be made larger in in three eyes (participant 3 left eye and participant 5 both eyes) as visual acuity was too poor to visualize the target. A minimum of two isopters for either eye was plotted. A full aperture lens was used to correct refractive error when required. Each isopter was digitally processed using image software (ImageJ, V1.48, <u>http://rsbweb.nih.gov/ij/index.html</u>)²⁶. As the nasal half of the visual field is smaller than the temporal half of the visual field in normals²⁷, the area of each half field could not be used to assess inter ocular differences, therefore the height of the visual field at the center to the largest target size tested was measured in degrees. Any visual field that crossed the midline was measured horizontally at the widest point in degrees.

Optical coherence tomography

Images of the optic nerve were taken using a spectral domain OCT (Spectralis Acquisition model 6.0.12.0 - Heidelberg Engineering Inc., Germany) with active eye tracking. The RNFL (retinal nerve fiber layer) optic disc protocol, consisting of one 3.5–3.6mm diameter circle scan was employed. Quality criteria included sharp scan

beam and definition of vessels, scan beam centered on optic disc, even illumination, and automatic real-time score of 16 or better. In two eyes with poor vision a moveable external fixation light was used as a target to achieve steady fixation. The RNFL was calculated as a global value and also dissected in to the automated 6 sections. The measurements are given in microns according to the calibration given by the manufacturers and were compared to normative data²⁸.

Pattern visually evoked potentials

prVEP recordings were carried out adhering to international standards ²⁹. The electroencephalogram was collected employing a three-channel montage. Three active electrodes (Oz, O1 and O2) were placed according to the 10:20 system referred to Fpz. The ground electrode was placed at POz. The impedance of the electrodes was maintained below $5k\Omega$ throughout the recording. The band pass setting of the digital filters was 0.3 to 100 Hz. To ensure reproducibility of the prVEP responses, a minimum of two trials with a minimum of 75 epochs were recorded. A grand average of these two trials was then created and analyzed.

Any refractive error correction was used for prVEP testing. Monocular responses were recorded for each eye for full field and half field stimulation. Stimuli consisted of a reversing checkerboard pattern at a rate of three reversals a second with checks of 97% contrast subtending 50 minutes of arc presented in a 28 degree field. The stimuli were displayed on a plasma display screen (Model PDP 433MXE –Pioneer Electronics Corp. Tokyo, Japan.) with a luminance of 65 cd/m² measured with a photometer (LS-110 - Konica Minolta, Shanghai). The center of the screen was positioned at eye level and at a distance of 1 meter in front of the participant. Participants were instructed to attend to a red central fixation spot, in order to maintain steady and central fixation. Fixation accuracy was also monitored via a close circuit TV system. Data acquisition was paused if any fixation loss was seen. For the full field responses the amplitude and latency of the pattern reversal stimulation the amplitude and latency of the p100 component was measured over the hemisphere ipsilateral to the visual field being stimulated.

Results:

Visual acuity was within normal limits in two participants (2 and 6). The visual acuity for each participant is displayed in figure 1 and table 1. As a group visual acuity was better in the eye ipsilateral to the side of surgery compared to the contralateral eye (t = 2.758, df = 5, P = 0.040, two tailed). A summary of binocular function for each participant is in table 1. Cover test in all participants revealed a divergent deviation. In participants 4 and 6 this was completely controlled as a small exophoria at near and distance while the other four participants had intermittent exotropia with variable degrees of size and control (participants 1,2,3 and 5). Those with intermittent exotropia had a fixation preference, and fixed with the eye ipsilateral to the side of hemispherectomy. Apart from participant 5 some level of near hemistereopsis could be demonstrated, and this was normal in participants 2 and 6. Participant 4 was noted to have an anomalous head posture and ocular motility testing revealed this was due to a congenital IV nerve palsy with his head turning and tilting to the opposite side. All other participants had full ocular movements. None of the participants had any clinically visible nystagmus.

<u>Visual fields</u>

Visual field assessment was achieved in all eyes. In two eyes (right eye of participants 3 and 5) only the largest brightest target (V4e) could be detected, therefore responses could not be reproduced to a different target. As expected all participants had homonymous hemianopia contralateral to the side of surgery. When compared to normative data, the functional half field was also reduced in all cases.

The height of visual field at the midline to the largest target tested was measured in all eyes in order to compare the two eyes of each participant. The measurements revealed a shorter height, and therefore greater constriction in the contralateral eye to side of surgery compared to the ipsilateral eye (t=2.62, df=5, p=0.047, 2 tailed) (fig 1).

The visual field extended past the midline into the blind field in eleven out of twelve eyes, with good central fixation observed throughout. This finding was mapped in different sensitivities to at least two target sizes in ten out of those eleven eyes (one eye could only see the largest target – V4e).

The maximal width across the midline into the blind half field averaged 4.1degrees (max 10.04 degrees, min 0.3 degrees) with a variable location with no preference for the macula. Interestingly the widest cross over the midline (10.04 degrees) being 40 degrees inferiorly.

In the one eye that obeyed the midline, previous visual fields 5.5 years post operatively revealed crossing at the midline, indicating a dramatic constriction some time between 5.5 years and 21 years post operatively (participant 3). All visual fields are shown in figure 2.

Pattern Visually evoked potentials

Monocular full field and half field pattern reversal visual evoked potentials were recorded in 5 of the 6 cases. In participant 5 no responses were evident above the level of noise. Comparisons of P100 full field and half field amplitudes and latencies were compared using paired T tests. There was a larger full field P100 component in the ipsilateral eye to surgery compared to contralateral eye [t = 2.90, df = 4, p =

0.044, 2-tailed] see figure 1. The crossing and non-crossing pathways were individually investigated using half field stimulation. Each half field for each eye evoked reproducible visual evoked potentials. Example waveforms and a reference slice from an axial MRI are shown for a right anatomical hemispherectomy and left functional hemispherectomy (figure 3). As expected responses evoked by stimulation of the residual visual field were larger in amplitude than evoked by those evoked by stimulation of the hemianopic field for each eye (ipsilateral eye to surgery [t = 2.79, df = 4, p = 0.049, 2-tailed], contralateral eye to surgery [t = 3.52, df = 4, p = 0.024, 2-tailed]). Further investigation revealed that the individual half fields responses were larger in the eye ipsilateral to surgery eye compared to the eye contralateral to side of surgery (ipsilateral half field [t = 2.99, df = 4, p = 0.040, 2tailed], contralateral field [t = 2.84, df = 4, p = 0.047, 2-tailed]). The amplitudes of the full field and half field responses for the 5 participants with recordable VEPs are tabulated in table 2.

Optical Coherence Tomography

High quality images of the RNFL were obtainable in all eyes. For every participant the global RNFL was statistically smaller in the contralateral eye compared to the ipsilateral eye (t = 4.893, df = 5, P = 0.004, two tailed) (figure 1). This was on average reduced by 14.47% (range 8.88-19.82%) in the contralateral eye compared to the ipsilateral eye.

The pattern of loss and sparing described in Hoyt's original work and later OCT work is evident in the OCT scans obtained in 8 of the tested eyes. The contralateral eyes have intact nerve fibers originating inferiorly and superiorly and the ipsilateral eyes have atrophic nerve fiber layer superiorly and inferiorly with residual functional nerve fiber layer being mostly the nasal fibers supplying the papulomacular bundle. (Figure 4). The remaining four eyes showing a pattern of more global nerve fiber layer loss. The group averages for each sector are shown in figure 4 and compared to normative data.

Discussion:

This study has demonstrated that in a group adults who have undergone hemispherectomy in childhood have better visual function including visual acuity and preserved visual field in the eye ipsilateral to the side of the hemispherectomy compared to the contralateral eye.

In our study, as previously reported, subjects who have undergone hemispherectomy were noted to have a divergent squint post surgery²⁵. None of our participants on questioning had a squint prior to surgery supporting the notion that the squint post-surgery is a compensatory mechanism to the resulting field defect. In our study the majority of the participants had an intermittent distance exotropia, with good control of exophoria at near and breaking down to be mostly exotropic at distance. This is believed to be an advantageous compensatory mechanism as they are potentially sacrificing binocularity for increased navigational visual field in the distance³⁰. The participants in our study who had a manifest squint had almost exclusively intermittent squint, which concurs with the theory this is a scanning mechanism³¹ rather than a constant deviation as a result of anomalous retinal correspondence³². In our study participants with the most preserved visual fields had controlled exophorias at near and distance with normal stereopsis, while those with very constricted fields had intermittent exotropia and reduced or absent near stereopsis. These findings support the notion that the compensatory squint is more likely to develop in people with more severely constricted visual fields. In our small group we did not observe any static or dynamic head posturing post operatively associated with the visual field defect. In Koenraads group this was observed in 53%²⁵, this may be due to the much larger cohort studied. However as the cohort had a shorter length of follow up, perhaps this mechanism is an earlier compensatory mechanism that is used less over time after surgery as they adapt. They also found it less in left sided hemispherotomies (for unexplained reasons). Although they proposed possible compensatory purposes, Brodsky has proposed that the abnormal head posture seen in congenital or early acquired hemianopia may be a 'heliotropic' response, relating to visual influence on muscle tonus rather than an adaptive response to centralize the field ³³.

The OCT findings in four of our participants showed the nerve fiber layer pattern described in Hoyt's original work^{9,10} and later OCT work ^{11,13,14} where the contralateral eye has intact nerve fibers originating interiorly and superiorly and thinner temporally and nasally and vice-versa for the ipsilateral eye. This pattern has recently also been reported in data from another group post hemispherectomy³⁴. In two participants a more global nerve fiber layer loss was observed. The global RNFL measures in our participants were greater in the ipsilateral eyes to hemispherectomy compared to the contralateral eye in each case. This may be due to the ipsilateral eye having a more uniformly distributed nerve fiber layer loss around the disc compared to the selective horizontal loss in the contralateral eye¹⁴. Although it is well documented that the outcome of hemispherectomy surgery will be a complete contralateral homonymous hemianopia our participants all unexpectedly showed constriction of the residual visual field of varying degrees of constriction. In one case (participant 3) serial visual fields at over a prolonged interval that preceded surgery and continued post-surgery demonstrate progressive

constriction of the residual half of visual field spanning 21 years after surgery (figure 2). This was an unexpected finding having not been previously described, and is of concern. Although visual field tests do show inter-test variability, this was a progressive change noted over separate visits, with good fixation documented and significantly larger targets having to be used in the more recent test. One possible explanation could be ongoing subclinical epileptic or background EEG abnormalities in the contralateral hemisphere. Such activity has previously been recorded and shown not to affect seizure outcome or postoperative cognitive performance³⁵. However no focal EEG activity was observed over the occipital regions during the acquisition of the VEP responses. Another possible explanation would be a spread of the anterograde degeneration from ganglion cell interactions in the retina or the lateral geniculate nucleus.

Despite the constriction of the visual fields in our participants residual functional visual field was evident beyond the midline into the blind half field in 11/12 eyes as previously reported^{19–24} and further supported electrophysiologically by the presence of prVEPs evoked by stimulation of the blind field. In the one eye where the visual field did not cross the midline at 21.1 years after surgery, it had previously been documented to cross at 5.5 years after surgery. Although half field prVEPs were not recorded at that time to support the presence of this in the blind half field, the absence of a half field response obtained under close monitoring of fixation supports the most recent fields that do not currently cross the midline. The responses from the blind half field were detected from electrodes more laterally over the remaining occipital lobe than those from the seeing half field suggesting they originate from a different generator location compared to those from the seeing half field. Further work using source analysis and a greater number of electrodes could be used to investigate this in relation to the post surgery brain anatomy.

In our group eyes contralateral to the side of hemispherectomy had poorer vision, greater constricted field and overall thinner retinal never fiber layer in comparison to ipsilateral eyes to surgery that had better visual acuity, size of field and preservation of nerve fiber layer. The difference in visual acuities between the eyes, was again an unexpected finding, having not been reported in other unilateral injuries to the visual cortex and requires further investigation.

Possible mechanisms include a greater representation of macular visual pathway in the contralateral cortex. Asymmetric crossing of macular pathway crossing at the chiasm has been reported in primates³⁶ but acuity differences are not generally seen in adults with homonymous hemianopia after stroke.

Another possibility is trophic preservation of the macular ganglion cells across the vertical raphe by parafoveal ganglion cells – it is possible that the ganglion cells which cross at the chiasm (and feed into the nasal and temporal part of the disc) have more of a trophic function than the uncrossed ganglion cells – it may take years of anterograde degeneration of ganglion cells following a unilateral cerebral injury for this effect to be seen. This would explain why inter-ocular difference in acuity is not reported in stroke and why it was not reported in the previous report of visual acuity outcome in children following hemispherectomy, whose median follow up was only 2.4 years.

Another possibility relates to amblyopia: most of these patients developed an intermittent distance exotropic deviation after undergoing the surgery in childhood

and it is possible that if this squint developed early, strabismic amblyopia may be the cause.

This study has small number of participants due to strict inclusion criteria, the bias of mostly left hemispherectomies, and lack of serial monitoring in all modalities. As a result further work with a larger cohort and range of post hemispherectomy follow up interval is needed to determine the time course of the progressive visual dysfunction. Detailed pre-operative assessment would also be needed to determine the presence of inter-ocular difference preoperatively given the congenital nature of the pathology in this group. The long term follow up of children of the same congenital pathologies who decline hemispherectomy surgery could also be used as a control group. It would also be of interest to investigate other unilateral pathologies affecting the visual pathways to determine if our findings are specific to children with congenital pathology who have undergone a hemispherectomy or evident in other types of unilateral visual pathway dysfunction such as stroke.

The long-term follow-up of our participants who had undergone hemispherectomy in childhood revealed significant visual deficits that were not expected. Although initial pathology may contribute to the dysfunction they may also be due to the longterm consequence of the initial surgery. Hemispherectomy remains a very effective treatment achieving seizure freedom for children where medication has failed. We suggest these patients who undergo hemispherectomy should be monitored by an ophthalmology team in case of deterioration and for appropriate ophthalmology management. They may also be eligible for visual impairment registration, which will give them access to support services. This will ultimately maximize their visual function and ultimately improve their quality of life.

Acknowledgements:

All of the authors have reviewed and revised this manuscript and declare:

- A) No funding or grant support was received for this project.
- B) No financial disclosures or conflicts of interest.
- C) No other acknowledgments.
- All authors attest they have met the current ICMJE criteria for authorship.

References:

- 1. Griessenauer CJ, Salam S, Hendrix P, et al. Hemispherectomy for treatment of refractory epilepsy in the pediatric age group: a systematic review. *J Neurosurg Pediactrics*. 2015;15(January):34-44.
- 2. Lee Y-J, Kim E-H, Yum M-S, Lee JK, Hong S, Ko T-S. Long-term outcomes of hemispheric disconnection in pediatric patients with intractable epilepsy. *J Clin Neurol*. 2014;10(2):101-107.
- 3. Patel DE, Cumberland PM, Walters BC, et al. Study of optimal perimetric testing in children (OPTIC): Feasibility, reliability and repeatability of perimetry in children. *PLoS One*. 2015;10(6):1-12.
- 4. Trobe JD, Acosta PC, Krischer JP, Trick GL. Confrontation visual field techniques in the detection of anterior visual pathway lesions. *Ann Neurol*. 1981;10(1):28-34.
- 5. Blumenhardt LD, Halliday a M. Hemisphere contributions to the composition of the pattern-evoked potential waveform. *Exp Brain Res.* 1979;36(1):53-69.
- 6. Mellow TB, Liasis A, Lyons R, Thompson D. When do asymmetrical full-field pattern reversal visual evoked potentials indicate visual pathway dysfunction in children? *Doc Ophthalmol*. 2011;122(1):9-18.
- 7. Blumhardt LD, Barett G, Halliday a M. The assymetrical visual evoked potential to pattern reversl in one half field and its significance for the analysis of visual field defects. *Br J Ophthalmol*. 1977;61:454-461.
- 8. Celesia GG, Meredith JT, Pluff K. Perimetry, visual evoked potentials and visual evoked spectrum array in homonymous hemianopia. *Electroencephalogr Clin Neurophysiol*. 1983;56:16-30.
- 9. Hoyt WF, Rios-Montenegro EN, Behrens MM, Eckelhoff RJ. Homonymous hemioptic hypoplasia Fundoscopic features in standard and red-free illumination in three patients with congenital hemiplegia. *Br J Ophthalmol.* 1972;56:537.
- 10. Hoyt WF. Ophthalmoscopy of the reinal nerve fibre layer in Neuro-Ophthalmologic Diagnosis. *Am J Ophthalmol.* 1976;4:14-34.
- 11. Herro AM, Lam BL. Retrograde degeneration of retinal ganglion cells in homonymous hemianopsia. *Clin Ophthalmol*. 2015;9:1057-1064.
- 12. Goto K, Miki A, Yamashita T, Araki S. Sectoral analysis of the retinal nerve fiber layer thinning and its association with visual field loss in homonymous hemianopia caused by post-geniculate lesions using spectral-domain optical coherence tomography. *Graefe's Arch Clin Exp Ophthalmol.* 2016;254:745-756.
- Mehta JS, Plant GT. Optical Coherence Tomography (OCT) Findings in Congenital/Long- Standing Homonymous Hemianopia. *Am J Ophthalmol*. 2005;(140):727-729.
- 14. Jindahra P, Petrie A, Plant GT. Retrograde trans-synaptic retinal ganglion cell loss identified by optical coherence tomography. *Brain*. 2009;132:628-634.

- 15. Vargha-Khadem F, Carr LJ, Isaacs E, Brett E, Adams C, Mishkin M. Onset of speech after left hemispherectomy in a nine-year-old boy. *Brain*. 1997;120(1):159-182.
- Liégeois F, Morgan AT, Stewart LH, Helen Cross J, Vogel AP, Vargha-Khadem F. Speech and oral motor profile after childhood hemispherectomy. *Brain Lang*. 2010;114(2):126-134.
- 17. Holloway V, Gadian DG, Vargha-Khadem F, Porter D a, Boyd SG, Connelly a. The reorganization of sensorimotor function in children after hemispherectomy. A functional MRI and somatosensory evoked potential study. *Brain*. 2000;123 Pt 12:2432-2444.
- Devlin a. M, Cross JH, Harkness W, et al. Clinical outcomes of hemispherectomy for epilepsy in childhood and adolescence. *Brain*. 2003;126(3):556-566.
- 19. Ptito a., Lassonde M, Lepore F, Ptito M. Visual discrimination in hemispherectomized patients. *Neuropsychologia*. 1987;25(6):869-879.
- 20. Perenin MT, Jeannerod M. Residual vision in cortically blind hemiphields. *Neuropsychologia*. 1975;13(1):1-7.
- 21. Wessinger CM, Fendrich R, Ptito a., Villemure JG, Gazzaniga MS. Residual vision with awareness in the field contralateral to a partial or complete functional hemispherectomy. *Neuropsychologia*. 1996;34(11):1129-1137.
- 22. Wessinger CM, Fendrich R, Gazzaniga MS, Ptito a, Villemure JG. Extrageniculostriate vision in humans: investigations with hemispherectomy patients. *Prog Brain Res.* 1996;112:405-413.
- 23. Werth R. Visual functions without the occipital lobe or after cerebral hemispherectomy in infancy. *Eur J Neurosci.* 2006;24(10):2932-2944.
- 24. Muckli L, Naumer MJ, Singer W. Bilateral visual field maps in a patient with only one hemisphere. *Proc Natl Acad Sci U S A*. 2009;106(31):13034-13039.
- 25. Koenraads Y, Van Der Linden DCP, Van Schooneveld MMJ, et al. Visual function and compensatory mechanisms for hemianopia after hemispherectomy in children. *Epilepsia*. 2014;55(6):909-917.
- 26. Schneider C a, Rasband WS, Eliceiri KW. NIH Image to ImageJ: 25 years of image analysis. *Nat Methods*. 2012;9(7):671-675.
- 27. Niederhauser S, Mojon DS. Normal isopter position in the peripheral visual field in Goldmann kinetic perimetry. *Ophthalmologica*. 2002;216(6):406-408.
- 28. Bendschneider D, Tornow RP, Horn FK, et al. Retinal Nerve Fiber Layer Thickness in Normals Measured by Spectral Domain OCT. *J Glaucoma*. 2010;19(7):475-482.
- 29. Odom JV, Bach M, Brigell M, et al. ISCEV standard for clinical visual evoked potentials (2009 update). *Doc Ophthalmol*. 2010;120(1):111-119.
- 30. Donahue SP, Haun AK. Exotropia and face turn in children with homonymous hemianopia. *J Neuroophthalmol*. 2007;27(4):304-307.
- 31. Jacobson L, Lennartsson F, Pansell T, Oqvist Seimyr G, Martin L. Mechanisms

compensating for visual field restriction in adolescents with damage to the. *Eye.* 2012;26(July):1437-1445.

- 32. Levy Y, Turetz J, Krakowski D, Hartmann B, Nemet P. Development of Compensating Exotropia With Anomalous Retinal Correspondence After Early Infancy in Congenital Homonymous Hemianopia. *J Pediatr Ophthalmol Strabismus*. 1995;32:236-238.
- 33. Brodsky MC. Latent heliotropism. Br J Ophthalmol. 2002;86:1327-1328.
- Audren F. Free Paper 18: Sectoral analysis of the retinal nerve fiber layer thinning after hemispherectomy. In: *The 42nd Annual Meeting of EPOS -European Paediatric Ophthalmological Society. Zurich Switzerland.* Vol Zurich; 2016.
- 35. Boshuisen K, Van Schooneveld MMJ, Leijten FSS, et al. Contralateral MRI abnormalities affect seizure and cognitive outcome after hemispherectomy. *Neurology*. 2010;2(November):1623-1630.
- Leventhal AG, Ault SJ, Vitek DJ. The Nasotemporal Division in Primate Retina : The Neural Bases of Macular Sparing and Splitting. *Science (80-)*. 1986;240(484):66-67.

Figure captions:

Figure 1: Ophthalmic findings in adults who have undergone hemispherectomy in childhood.

An inter ocular difference is evident with eyes ipsilateral to the side of surgery being better than contralateral eyes. This could be seen in (top left) best corrected visual acuity; (top right) Goldmann visual field height at the midline to the largest target seen by participants; (bottom left) P100 amplitude of the pattern reversal VEP in response to full field stimulation employing a 50 arc min test check and (bottom right) global retinal nerve fiber layer of the optic nerve on optical coherence tomography.

Figure 2. The monocular Goldmann visual fields of participant 3 before and after hemispherectomy surgery.

Pre-op in dashed line (IV4e target), 5.5 years postoperative in spotted line (I4e target) and 21.1 years postoperative in solid line (V4e target – largest and brightest). Though different targets are used there is a significant deterioration from 5.5 years post operatively to 21.1 years post operatively evident.

Figure 3. Visually evoked potentials from two participants who underwent hemispherectomy.

(Top left) Axial slice of MRI scan from participant 6 who underwent a left functional hemispherectomy demonstrating the disconnected left hemisphere resulting in a right homonymous hemianopia. (Bottom left) Axial slice MRI scan from participant 4 who underwent a right anatomical hemispherectomy and has a left homonymous hemianopia.

Full field (FF) pattern reversal visually evoked potentials, right half field (RHF) and left half field (LHF) evoked potentials for both participants (Top right participant 6 and bottom right participant 4). The right eye is shown in a solid line and left eye in a dashed line. The solid black triangles indicate the ipsilateral p100 from the seeing half field and the un-shaded white triangles indicate the ipsilateral p100 from the blind half field.

Figure 4. The Average nerve fiber layer measurement of all participants compared to control data from six quadrants for each eye in micrometers (um). (left) Eyes ipsilateral to side of surgery and (right) contralateral to side of surgery. The participant's grouped data is shown in the hatched boxes and compared to normative data in the solid boxes. The difference in distribution between the ipsilateral and contralateral eyes is evident. indicates segments where the standard deviation of the participants and normal data do not cross.

Table 1. Etiology and clinical findings of all participants who underwent hemispherectomy in childhood.

Р	S	Sex	Etiology	SOS	SOHH	TOS	AAS	F-up	VA-I	VA-C	NAD	ND	DAD	DD	N-St
1	٠	М	Sturge Weber	Left	Right	Functional	8.5	25.0	0.100	0.400	10	<u>X(</u> T)	25	RX(<u>T</u>)	110
2		F	Congenital Stroke	Left	Right	Functional	10.5	21.8	0.060	0.040	16	R <u>X(</u> T)	8	RX(<u>T</u>)	85
3	\diamond	F	Refractive Epilepsy	Left	Right	Functional	13.8	21.2	0.300	0.720	40	<u>X(</u> T)	25	Х <u>(Т</u>)	600
4		М	Hemimegancephaly	Right	Left	Anatomical	4.2	19.4	0.040	0.440	10	Х	8	Х	110
5	×	F	Dysplastic left hemisphere	Left	Right	Functional	2.3	28.8	0.060	0.700	10	R <u>X(</u> T)	16	RXT	0
6	∇	М	Middle cerebral artery infarct	Left	Right	Functional	15.1	6.4	-0.040	-0.040	20	Х	6	Х	55
						Average	9.1	20.4	0.087	0.377	17.7		14.7		160
						Max	15.1	28.8	0.300	0.720	40		25		600
						Min	2.3	6.4	-0.040	-0.040	10		6		0

P = participants; S = participant symbol; SOS = Side of surgery; SOHH = Side of homonymous hemianopia; TOS = Type of surgery; AAS = Age at surgery; F-up = Years since surgery; VA-I = Visual acuity in eye ipsilateral to side of surgery; VA-C = Visual acuity in eye contralateral to side of surgery; NAD = Near angle of deviation in diopters; ND = Type of near deviation; DAD = Distance angle of deviation in diopters; DD = distance deviation type; N-St = near stereopsis in seconds of arc. X = Exophoria; XT = Exotropia; X(T) = intermittent exotropia; X = Deviation latent greater than manifest; T = Deviation manifest greater than latent; R = Right eye.

CERTER

Table 2. Amplitude of the pattern reversal visual evoked potential P100 component evoked by full field and half field monocular stimulation of eyes ipsilateral and contralateral to the side of hemispherectomy.

Eye	Full field P100 (uV) ± SE	Ipsilateral field P100 (uV) ± SE	Contralateral field P100 (uV) ± SE
Ipsilateral	6.0±2.4	5.5±1.3	3.5±0.7
Contralateral	3.0±3.6	3.0±0.9	2.0±0.6
			Q -'
		\rightarrow	
		\sim	
, y			











