Brain structure in children with congenital visual disorders and visual impairment

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This article is commented on by Bauer on page 16 of this issue.

A large proportion of the cortex is dedicated to the processing of visual information in typically sighted children and adults. Visual experience in development appears vital for establishing the necessary architecture in visual cortical areas that support visual processing throughout life.1 In cases where children are born with disorders that affect the sensory part of the visual system, the majority are medically untreatable with immediate and chronic absent or reduced vision. While the central nervous system (CNS) is not anticipated to be directly affected in the aetiology of many congenital disorders affecting the peripheral visual or ocular system,2 brain structure and function may adjust or be compromised after the visual deprivation caused by the deficits in the sensory parts. The current study therefore aimed to investigate if there are differences in brain anatomy in school-aged children born with disorders of the peripheral visual system. It was hypothesized that severity of visual impairment may also have an influence on brain development.

Congenital visual impairment has been found to be associated with several structural and functional brain differences in adulthood. The strongest effects have been found in neural structures that are involved in visual processing. The optic nerve and optic chiasm are reduced in volume, as well as alterations in microstructural organization of their white matter.3 Thalamic nuclei that are typically involved in the transmission of visual information show reorganization in animal models,4 and appear smaller on structural magnetic resonance imaging (MRI) of adults with anophthalmia.5 The optic radiations that transfer visual information between the thalamus and the primary visual cortex are reduced in size and show reductions in microstructural integrity.6,7 The primary visual cortex also shows a different morphology of reduced grey matter content, reduced cortical surface area, and increased cortical thickness.3,8 Even cortical areas that are associated with higher-order visual processing have shown anatomical differences.6,9 Most of this brain research focused on those who are defined as ‘blind’, which encompasses those who are Braille users with estimated visual acuity of 3/60 (logMAR 1.3) or worse,10 and did not examine the outcomes of differing levels of visual impairment, including mild-to-moderate ranges.

We investigated the relationship of congenital visual impairment with structural brain organization during middle childhood and, specifically, compared the brain organization associated with differing levels of visual impairment. The study focused on children aged 8 to 12 years who had
congenital disorders of the peripheral visual system (CDPVS), i.e. disorders of the globe, retina, or anterior optic nerve, and vision level of severe visual impairment (SVI) or mild-to-moderate visual impairment (MVI). According to the existing adult literature, we predicted differences in brain structures, particularly in regions associated with vision processing, in children with visual impairment versus those with typical sight and greater differences in those with SVI versus MVI. In addition to whole-brain comparisons, we focused on the thalamus, optic radiations, and corpus callosum, as highlighted in the adult literature.

**METHOD**

**Participants**

The analysis presented here were part of a wider cross-sectional study on the neural and cognitive sequelae of congenital visual impairment during mid-childhood. This study was performed in accordance with the Declaration of Helsinki. The study was approved by the National Health Service Research Ethics Committee (12/LO/0939). All parents provided written informed consent for participation and publication of results, and children provided verbal assent for participation.

The inclusion criteria were as follows: (1) children with CDPVS and no other known CNS disorder in the paediatric diagnosis, according to ophthalmological report; (2) age 8 to 12 years; (3) congenital visual impairment, with estimated best-corrected visual acuity of logMAR 0.6 or worse; (4) verbal IQ greater than 75 or attending mainstream school and performing at age-appropriate level; and (5) English as their first language. Exclusion criteria were preterm birth (<37wks’ gestational age), cerebral visual impairment, ‘complex’ CDPVS (including known CNS involvement), endocrine abnormalities, epilepsy, and additional neurological impairments, e.g. motor.

Recruitment was undertaken through initial identification via the patient database of the tertiary developmental vision neurodisability clinic (Great Ormond Street Hospital for Children), which is the primary research site, or the local collaborator of a tertiary children’s eye hospital (Moorfields Eye Hospital) and an open recruitment call through charitable and educational agencies associated with vision neurodisability clinics (ND or collaborator).

In the wider study, 18 children with visual impairment consented (via parents) to participate over the duration of the study (2012–2014). Twelve of the children with visual impairment participated in this part of the study. The remaining six children did not participate because their parents were concerned about safety or time commitment. Of those participating, two (one with MVI, one with SVI) had to be excluded from final analysis owing to poor data quality. The final sample consisted of five children with SVI (two females, mean age 10y 5mo [SD 10mo], range 10–12y; see Table I), five with MVI (two females, mean age 10y 4mo [SD 1y 7mo], range 8–12y), and 21 TSC children (11 females, mean age 10y 10mo [SD 2y], range 8–13y). There was no significant difference in age between the groups (one-way analysis of variance: F[2,29]=0.23, p=0.796). No differences in movement (maximum frame-wise displacement) were found between the vision level

| Table I: Characteristics of children with visual impairment |
|-----------------------------------------------------------|
| **Case** | **Sex** | **Age (y)** | **logMAR** | **Near detection** | **Visual Disorder** |
| MVI1 | Male | 12 | 0.6 | – | Rod-cone dystrophy |
| MVI2 | Female | 8 | 0.6 | – | Oculocutaneous albinism |
| MVI3 | Male | 12 | 0.6 | – | Congenital nystagmus |
| MVI4 | Male | 10 | 0.7 | – | Ocular albinism, congenital nystagmus |
| MVI5 | Female | 12 | Left: 0.23, right: light perception only | Unilateral optic nerve hypoplasia |
| SVI1 | Male | 12 | 0.9 | – | Oculocutaneous albinism |
| SVI2 | Male | 10 | 1.2 | – | Leber congenital amaurosis |
| SVI3 | Male | 10 | 1.225 | – | Norrie disease |
| SVI4 | Female | 11 | 1.5cm ‘lure’ from 20cm | – | Leber congenital amaurosis |
| SVI5 | Female | 10 | 12.5cm ‘lure’ from 50cm | – | Bilateral microphthalmia |

MVI, mild-to-moderate visual impairment; SVI, severe visual impairment.
groups (mean SVI 0.84 [standard error {SE} 0.05]; mean MVI 0.8 [SE 0.1]; mean TSC 0.81 [SE 0.09]; $F_{2,28} = 0.02$, $p = 0.981$).

**Measures**

**Vision level**
The experimenter (JB) was trained by a paediatrician specialized in visual impairment to assess visual acuity using the Sonksen logMAR test. Distance acuity at 3m was measured with both eyes open and with corrective glasses if the child regularly wore glasses. Two children with SVI, defined here as vision level of logMAR greater than 0.8, could not identify the largest optotypes on the Sonksen logMAR test (>1.65 logMAR) and were therefore assessed on the Near Detection Scale (cases SVI4 and SVI5, see Table I). MVI was defined here as vision level of 0.6 to 0.8 logMAR.

**MRI data acquisition**
All scans were performed on a Siemens Avanto 1.5 T clinical system (Siemens Healthcare, Erlangen, Germany), using a self-shielding gradient set with maximum gradient strength of 40mT/m and a 32-channel quadrature head coil. T1-weighted volume scans were acquired using a whole-brain coverage three-dimensional fast low angle shot structural image acquired at 1mm$^3$ image resolution (echo time: 4.9ms; repetition time: 11ms). Diffusion MRI was acquired using echo-planar diffusion-weighted images with an isotropic set of 60 non-collinear directions at $b=1000s/mm^2$, interleaved with four b0 volumes. Whole-brain coverage was obtained with 60 contiguous axial slices at 2.5mm$^3$ resolution (echo time: 89ms; repetition time: 7300ms).

**Voxel-based morphometry**
Whole-brain voxelwise comparison of grey matter compartments were performed. Local differences in grey matter volume were analysed with the voxel-based morphometry pipeline part of the FMRIB Software Library (FSL), an optimized VBM protocol carried out with FSL tools. The modulated grey matter images were smoothed with an isotropic Gaussian kernel at sigma 3mm. Similar results were obtained at 2mm and 4mm. Group comparisons were carried out using permutation $t$-tests with 10 000 permutations and cluster-free threshold enhancement to correct for multiple comparisons using FSL randomise.

**Thalamus volume**
To obtain the volume of the thalamus, a model-based segmentation and registration approach was used (FSL FIRST). Accurate segmentation of the thalamus was visually inspected for all participants. The total brain volume for each participant was obtained using FSL SIENA. The relative thalamus volume was calculated by dividing the thalamus volume by the total brain volume.

**Processing of diffusion MRI data**
Diffusion-weighted imaging allows the quantification of water diffusion in tissue in vivo. Correction for eddy current induced artefacts, motion, and field inhomogeneities were applied using the FSL eddy. Susceptibility artefacts were corrected with FSL topup using the b0 images. The images were then submitted to a non-local means denoising algorithm in the Diffusion Imaging in Python (DiPy) v0.8.0 package to boost the signal-to-noise ratio. Next, a brain mask of the b0 image was created using FSL BET. White matter integrity was quantified as fractional anisotropy.

**Tract-based spatial statistics**
Differences in white matter integrity were compared between the groups using tract-based spatial statistics. Group comparisons were carried out using FSL randomise with 10000 permutations and cluster-free threshold enhancement.

**Tractography of the optic radiation and posterior corpus callosum**
For reconstruction of the optic radiation, seed and inclusion regions were defined on fractional anisotropy maps for each participant in subject space. Specifically, a spherical seed region of interest (ROI) with a 3mm radius was defined in the white matter adjacent to the thalamus (see Fig. 1). A second ROI with a 6mm radius was placed in the white matter adjacent to the lateral ventricles a few slices dorsally from the seed ROI. Another inclusion ROI with 20mm radius was placed in the occipital lobe centred near the calcarine fissure. Exclusion ROIs were placed at the level of the anterior tip of the brain stem in axial view, ventrally to exclude streamlines of the corticospinal tract, and along the midline to avoid fibres of the corpus callosum. In addition, a brain mask was used for exclusion.

For reconstruction of the posterior corpus callosum (PCC), a seed mask was defined on the posterior quarter of the corpus callosum on a sagittal slice. To define the posterior quarter, the number of voxels greater than 0.1 fractional anisotropy were counted on a medial slice and divided into equal-length parts (see Fig. 1). This segment of the corpus callosum has been found to mostly contain fibres from visual areas in both hemispheres. In addition, an inclusion ROI consisting of a 20mm sphere placed over the medial occipital cortex was defined in each hemisphere.

Probabilistic tracking was performed based on a constrained spherical deconvolution model in MRTrix, with a target of 1000 streamlines, step size of 0.2mm, maximum curvature of 1mm and minimum/maximum length of 10mm/200mm. Streamlines were set to terminate in voxels with fractional anisotropy <0.1 or when hitting an exclusion mask. After probabilistic tracking, a visitation map of all voxels that contained at least 100 streamlines was calculated. This cut-off produced a satisfactory reconstruction of the optic radiations and PCC in all participants.
Statistical analysis
Because vision was assessed with different assessments, owing to children with very low vision not seeing the log-MAR optotypes, that do not translate into a single continuous measure of acuity, statistical models used group comparisons between children with SVI, MVI, or typical sight rather than using visual acuity as a continuous variable. Statistical comparisons of ROI values were based on the Kruskal–Wallis test with a factor for group (SVI, MVI, TSC) followed by a post hoc Dunn test for group contrasts carried out using the scikit-posthocs package v0.6.1 for Python. A significance threshold of $p_{corrected} < 0.05$ was set for all analyses. Bonferroni correction was used to account for multiple comparisons.

RESULTS

Participant characteristics
Table I shows characteristics of degree of visual impairment, visual disorder, etc. In the MVI group, one child had better vision than the MVI range in one eye (MVI5). In the SVI group two children were in the ‘blind’ range (vision of 1.3 logMAR or worse: SVI4 and SVI5), but they had some minimal detection vision.

Anatomical MRI scans were obtained from the 10 children with visual impairment; visual inspection of the images indicated no gross structural abnormalities in eight of the 10 children. Reduction of the right optic nerve was apparent in one child; small eyes were apparent in another child (see Table I for diagnostic information).

Whole-brain comparison of grey matter volume
There was no statistically significant difference in total grey matter volume between the vision groups (SVI: mean 904.26cm$^3$ [SE 38.84cm$^3$]; MVI: mean 982.45cm$^3$ [SE 41.62cm$^3$]; TSC: mean 1000.44cm$^3$ [SE 10.95cm$^3$]; MVI vs TSC: $p=0.454$; SVI vs MVI: $p=0.745$). There was a trend-level difference in total grey matter with lower values in the SVI group than in the TSC group (SVI vs TSC: $p=0.091$).

Voxelwise comparison indicated no significant between-group differences after correction for multiple comparisons. The corrected statistical map showed a cluster of decreased grey matter in the SVI group versus TSC at $p_{corrected}=0.08$. This cluster was adjacent to the optic radiations and seemed to extend into the white matter, indicating that this may be an artefact of white matter differences.

Comparison of thalamus volume
The volume of the thalamus was compared between the vision groups. Statistical comparison indicated a trend-level difference between the groups for the relative volume of the left thalamus (Kruskal–Wallis test: $H=5.29$, $p=0.071$). Follow-up contrasts indicated a smaller left thalamus volume, corrected for whole-brain volume, in the SVI group versus the TSC group ($p_{corrected}=0.047$, see Table II). No differences were indicated for the right thalamus (Kruskal–Wallis test: $H=2.81$, $p=0.245$).

Whole-brain comparison of white matter microstructure
There was no significant difference between the groups in total white matter volume (SVI: mean 5911mm$^3$ [SE 482mm$^3$]; MVI: mean 5525mm$^3$ [SE 113mm$^3$]; TSC: mean 5983mm$^3$ [SE 184mm$^3$] [$H=3.66$, $p=0.159$]). Differences in white matter microstructural organization across the whole brain were investigated. Tract-based spatial statistics analysis indicated a significant reduction of fractional anisotropy around the optic radiations and the PCC in the SVI group compared with TSC (see Fig. 2; statistics using cluster-free threshold enhancement – left optic radiation: $p_{corrected}=0.048$; right optic radiation: $p_{corrected}=0.006$, PCC: $p_{corrected}=0.038$). There were no significant differences after correction for multiple comparisons for the MVI versus TSC, or MVI versus SVI comparisons.

Tractography of the optic radiations and PCC
Statistical analysis of fractional anisotropy within the reconstructed optic radiations indicated significant
differences between the groups (Kruskal–Wallis test, left optic radiation: $H=9.38 \ [p=0.009]$; right optic radiation $H=11.81 \ [p=0.003]$). Follow-up contrasts indicated lower fractional anisotropy in the SVI than in the TSC group in the left and right optic radiations (see Table III). When excluding one apparent extreme data point in the MVI...
Comparison of fractional anisotropy within the optic radiations

|                   | Left optic radiation | Right optic radiation |
|-------------------|----------------------|-----------------------|
|                   | Mean | SE  | Mean | SE  |  |
| SVI               | 0.38 | 0.029 | 0.35 | 0.015 |  |
| MVI               | 0.34 | 0.030 | 0.36 | 0.029 |  |
| TSC               | 0.42 | 0.007 | 0.40 | 0.007 |  |

Comparison | $p$ | $p$ |
|-----------|----|----|
| SVI vs TSC | 0.002 | 0.006 |
| MVI vs TSC | 0.055 | 0.055 |
| SVI vs MVI | 0.347 | 0.754 |

Bold type indicates significance. SE, standard error; SVI, severe visual impairment; MVI, mild-to-moderate visual impairment; TSC, typically sighted comparison.

Table IV: Comparison of fractional anisotropy within the posterior corpus callosum

|                   | Mean | SE  |
|-------------------|------|-----|
| SVI               | 0.37 | 0.019 |
| MVI               | 0.46 | 0.038 |
| TSC               | 0.42 | 0.009 |

Comparison | $t$ | $p$ |
|-----------|----|----|
| SVI vs TSC | –2.75 | 0.025 |
| MVI vs TSC | 1.35 | 0.495 |
| SVI vs MVI | –2.11 | 0.047 |

Bonferroni-corrected $p$-values are reported. Bold type indicates significance. SE, standard error; SVI, severe visual impairment; MVI, mild-to-moderate visual impairment; TSC, typically sighted comparison.

distributed with a significant difference between the MVI and TSC group in the left and right optic radiations (left: mean 0.39 [SE 0.005; $p=0.003$]; right: mean 0.37 [SE 0.003; $p=0.006$]).

Comparison of fractional anisotropy within the PCC indicated a significant difference between the groups (Kruskal–Wallis test: $H=5.98$; $p=0.04$). Follow-up contrasts showed a reduction in the SVI group versus the TSC group and the MVI group (see Table IV). Other comparisons did not reach the significance criterion.

**DISCUSSION**

This study investigated whether school-aged children with CDPVS show differences in structural brain organization related to the severity of their visual impairment compared with age-matched TSC children. The sample comprised a group of children with MVI and a group of children with SVI, including some children in the ‘blind’ range according to World Health Organization definitions. The most pronounced differences were found in white matter microstructuralorganization of the optic radiations and the PCC in children with SVI. There was also a significant reduction in relative volume of the left thalamus in children with SVI. Children with MVI showed no consistent differences compared with the TSC group. The reduction in thalamus volume in children with SVI is in line with other investigations in specific vision disorders. In contrast to other studies, the current investigation did not find significantly reduced grey matter volume around the occipital cortex in the two visual impairment groups. The white matter differences indicated in the optic radiations and PCC are consistent with the findings in the adult literature with SVI/‘blind’ levels of vision. This provides further evidence to support the association of SVI with wall constraints in the development of the white matter structures of the posterior visual system. This association may be related to prolonged maturation of the white matter visual system after birth and its dependency on visual experience for full maturation. There may be differences in white matter integrity at least in some children, which may reflect earlier severity of visual impairment in infancy and the first year of life, and which warrants further investigation in a longitudinal sample. Differences in the neuroanatomical organization in MVI would also be expected based on reports in other samples of children at risk of visual impairment, e.g. in the context of preterm birth or hormone deficiency.

The strengths of this study are the taxonomic clarity of including only children with CDPVS and no other brain involvement according to their paediatric report, a relatively narrow age range of middle childhood, precise measurement of vision level and comparison between SVI and MVI, and application of well-validated MRI methods. However, the current study has limitations which may affect generalization of the findings. First, the sample size was limited to very small subgroups for each level of visual impairment, due to the challenge of recruiting children with CDPVS and no other brain involvement or intellectual disability and time constraints of the project. Second, to reach a minimum sample size, a range of disorders were included. The individual disorders are extremely rare and heterogeneous with often little-understood and complex genetic causes that may influence the brain phenotype. The results obtained with this small sample need to be replicated in larger samples, e.g. through international consortia of rare disorder research. Third, no child had profound visual impairment without vision at all, which may have very specific constraining effects on development and associated brain organization.

In conclusion, the current study provides first evidence that SVI is associated with reduced white matter microstructural organization in tracts of the brain’s visual system (optic radiations, posterior corpus callosum) and differences in thalamus volume in mid-childhood. These findings suggest that the organization of central visual structures is influenced by the quantity or quality of sensory visual inputs during development before mid-childhood.

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