Language networks in anophthalmia: maintained hierarchy of processing in ‘visual’ cortex

Kate E. Watkins,1,2 Alan Cowey,2 Iona Alexander,2 Nicola Filippini,1,3 James M. Kennedy,1 Stephen M. Smith,1 Nicola Ragge4,5 and Holly Bridge1

1 Oxford Centre for Functional MRI of the Brain (FMRIB), Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, OX3 9DU, UK
2 Department of Experimental Psychology, University of Oxford, Oxford, OX1 3UD, UK
3 Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, OX3 7JX, UK
4 Department of Biological and Medical Sciences, Oxford Brookes University, Oxford, OX3 0BP, UK
5 Wessex Regional Genetics Service, Princess Anne Hospital, Southampton and Faculty of Medicine, University of Southampton, Southampton, SO17 1BJ, UK

Correspondence to: Dr Kate Watkins,
Department of Experimental Psychology,
University of Oxford, South Parks Road, Oxford, OX1 3UD, UK,
E-mail: kate.watkins@psy.ox.ac.uk

Imaging studies in blind subjects have consistently shown that sensory and cognitive tasks evoke activity in the occipital cortex, which is normally visual. The precise areas involved and degree of activation are dependent upon the cause and age of onset of blindness. Here, we investigated the cortical language network at rest and during an auditory covert naming task in five bilaterally anophthalmic subjects, who have never received visual input. When listening to auditory definitions and covertly retrieving words, these subjects activated lateral occipital cortex bilaterally in addition to the language areas activated in sighted controls. This activity was significantly greater than that present in a control condition of listening to reversed speech. The lateral occipital cortex was also recruited into a left-lateralized resting-state network that usually comprises anterior and posterior language areas. Levels of activation to the auditory naming and reversed speech conditions did not differ in the calcarine (striate) cortex. This primary ‘visual’ cortex was not recruited to the left-lateralized resting-state network and showed high interhemispheric correlation of activity at rest, as is typically seen in unimodal cortical areas. In contrast, the interhemispheric correlation of resting activity in extrastriate areas was reduced in anophthalmia to the level of cortical areas that are heteromodal, such as the inferior frontal gyrus. Previous imaging studies in the congenitally blind show that primary visual cortex is activated in higher-order tasks, such as language and memory to a greater extent than during more basic sensory processing, resulting in a reversal of the normal hierarchy of functional organization across ‘visual’ areas. Our data do not support such a pattern of organization in anophthalmia. Instead, the patterns of activity during task and the functional connectivity at rest are consistent with the known hierarchy of processing in these areas normally seen for vision. The differences in cortical organization between bilateral anophthalmia and other forms of congenital blindness are considered to be due to the total absence of stimulation in ‘visual’ cortex by light or retinal activity in the former condition, and suggests development of subcortical auditory input to the geniculo-striate pathway.

Keywords: functional reorganization; cross-modal plasticity; functional MRI; vision; congenital blindness
Introduction

In total blindness, even with onset as late as 50 years (Rao et al., 2007), cortex normally dedicated to visual processing is activated by stimulation in the other intact sensory modalities (Merabet and Pascual-Leone, 2010). It has been suggested that this cross-modal reorganization of function may underlie enhanced tactile, auditory and verbal memory abilities (Van Boven et al., 2000; Amedi et al., 2003; Gougoux et al., 2004). Interference studies using transcranial magnetic stimulation and acquired lesions indicate that the functional activity of occipital cortex revealed by correlational imaging methods contributes to task processing and is not epiphenomenal (Cohen et al., 1997; Hamilton et al., 2000; Amedi et al., 2004). Whether this reorganization in the blind is attributable to changes in corticocortical or thalamocortical connectivity is unclear (Klinge et al., 2010) but might depend on the age at which visual input is lost (Burton et al., 2002a).

Bilateral anophthalmia represents the most extreme example of visual deprivation. In these rare individuals, both eyes fail to develop and retinal input to the visual system is absent. Our previous structural imaging study of the brain in anophthalmia revealed minimal structural cortical reorganization at the macroscopic level, with most of the occipital cortex showing no significant reduction in volume (Bridge et al., 2009). Instead, our data showed reorganization in the microstructure of white matter in anophthalmia, which was reflected in decreased fractional anisotropy and increased numbers of crossing fibres in the optic radiations compared to sighted controls. Whether such a pattern results from subcortical reorganization or is more consistent with the cortical pattern seen in other cases of early blindness (Noppeney et al., 2005; Fuji et al., 2009) is still unknown.

Functionally, the hierarchy of activation from the non-retinotopic lateral occipital complex, through extrastriate visual areas (V2–V4) to primary visual cortex (V1) has been described as ‘reversed’ in the blind, with striate cortex, V1, activated preferentially by higher-order cognitive tasks of language and memory rather than by Braille reading, and the opposite pattern of activity in lateral occipital complex (Amedi et al., 2003; Buchel, 2003). In most cases of developmental blindness, however, the eyes are present and some light-induced or even spontaneous activity along the pathways from the eye to subcortical relays and visual cortex is likely to have occurred before the onset of blindness. Consequently, the pattern of functional organization in anophthalmia might differ from that described even in congenital blindness. Such a phenotypic difference is supported by established differences between anophthalmic and enucleated mice models of congenital blindness, which are presumed to reflect prenatal spontaneous retinal activity in the enucleated mice (Chabot et al., 2007).

Here, we investigated the functional organization of the brain in five subjects with bilateral clinical anophthalmia. Their activation patterns were compared with those of sighted controls while they performed an auditory language task. To the best of our knowledge, this is the first report of task-related brain function in clinical anophthalmia. In addition, we examined the anophthalmic subjects for differences in resting-state networks identified from functional MRI data obtained during rest. Resting-state networks comprise functionally connected brain regions showing correlated fluctuations in the blood oxygen level-dependent (BOLD) signal, reflecting synchronous spontaneous neuronal activity (Biswal et al., 1995; Greicius et al., 2003). Examination of resting-state networks in anophthalmia allows us to assess whether extreme visual deprivation that results in functional reorganization at task also affects the ontogenesis of the brain’s resting functional architecture.

Materials and methods

Participants

Five subjects with isolated (i.e. with no other systemic manifestations) bilateral anophthalmia were scanned (age range 20–33 years; two female). One male also had dysplastic kidneys and a mild systolic murmur. A female subject had a cyst in her right orbit. All five were neurologically normal apart from their blindness and all read Braille. They are high-functioning adults who are in or have completed further or higher education. They previously participated in a structural imaging study (Bridge et al., 2009), where they were referred to as Cases 2, 3, 4, 5 and 6. The data reported here were acquired 24 months after the previous study; Case 1, from that study, was not scanned again.

Eighteen age-matched sighted controls (age range 20–35 years; nine female) were also scanned (six of the controls completed the task and resting-state functional MRI; six completed the task functional MRI only and another six the resting-state functional MRI only). All controls were either in or had completed higher education and had normal or corrected-to-normal vision. The study was conducted under ethical approval from the Oxfordshire NHS Research Ethics Committee (07/Q1605/20) and in accordance with the Declaration of Helsinki; all subjects provided informed, written consent. Braille documents were given to the anophthalmic subjects.

Image acquisition and analysis

Subjects were scanned using a 3-T Siemens Trio with a 12-channel head coil. Sighted controls kept their eyes closed and all were scanned in darkness. For the functional task (five anophthalmic subjects and 12 controls), we used a modified version of an auditory response-naming task (Bookheimer et al., 1998), which involved covert retrieval of a word from a three-word auditory description, e.g. ‘bees make it’. Activation to this auditory naming condition was contrasted with passive listening to digitally reversed versions of the auditory phrases and with a baseline during which no stimuli occurred and only background scanner noise was heard (‘Rest’ condition). Participants were instructed not to overtly speak the target word but to ‘think of the word inside their heads’. Stimuli were presented over MRI-compatible headphones (Nordic NeuroLabs) at a comfortable listening level. The Auditory Naming, Reversed Speech and Rest conditions were presented in 30-s blocks and repeated four times each in a fixed pseudorandom order, with no condition repeated consecutively. Each 30-s block of the Auditory Naming and Reversed Speech conditions had six stimuli, presented once every 5 s. Whole-head T2-weighted echo-planar images (echo time = 30 ms) were acquired every 3 s for
6 min (120 volumes). Each volume comprised 43 3-mm axial slices (in-plane resolution 3 × 3 mm).

Functional data from each individual were analysed using FEAT (v5.98), part of FSL (FMRIB’s software library; http://www.fmrib.ox.ac.uk/fsl). The images were motion corrected by realignment to the middle time point volume of the 4D data set, smoothed using a 6-mm full-width at half-maximum smoothing kernel, and non-linearly registered via the subject’s T1-weighted structural image to the MNI-152 template using FMRIB’s non-linear image registration tool in FSL. Low-frequency fluctuations were removed using a high-pass filter with a cut-off at 100 s. The motion correction parameters (translations and rotations in x, y and z) were included as covariates of no interest in the analyses. The Auditory Naming and Reversed Speech conditions were each contrasted with the Rest condition and with each other. Group averages and differences between groups for each of these contrasts were calculated in a second-level analysis using FMRIB’s Local Analysis of Mixed Effects (FLAME) stage 1 (Woolrich et al., 2004). Images were cluster-thresholded at $Z > 3.1$, and clusters were reported that survived a statistical test for extent ($P < 0.05$, fully corrected for multiple comparisons). This analysis revealed robust group differences for the basic contrasts of Auditory Naming versus Rest and Reversed Speech versus Rest. To look for group differences in the Auditory Naming versus Reversed Speech contrast, we used a slightly lower cluster-forming threshold ($Z > 2.3, P < 0.01$ cluster corrected). At the higher cluster-forming threshold of $Z > 3.1$, the differences in activation between these two conditions were not sufficiently large enough in the anophthalmia group to pass the extent threshold.

To examine the pattern of activation within the occipital cortex, mean percentage signal change for the Auditory Naming and Reversed Speech contrasts with Rest was calculated in small regions of interest in individual subjects. The regions of interest V1, V2, V3, V4 and V3A were retinotopically defined visual areas extracted from a probabilistic atlas based on retinotopic mapping in 18 sighted control subjects (Bridge, 2011). The lateral occipital complex was defined by comparing the activation to objects with that to scrambled pictures in a different group of eight sighted subjects. Primary auditory cortex (A1) and inferior frontal gyrus regions of interest were selected as control areas derived from the cytoarchitectonic probabilistic maps from the Juelich histological atlas (part of FSL). Areas TE1.0, TE1.1 and TE1.2 (Morosan et al., 2001) were combined to create left and right primary auditory cortex (A1) regions of interest; lateral frontal areas 44 and 45 (Amunts et al., 1999) were combined to make the left and right inferior frontal gyrus regions of interest. In each case, the region of interest comprised voxels present in >30% of subjects. These areas are displayed on an inflated surface in Fig. 1 for reference with the results from the analyses described below. The activity levels in these regions of interest were compared between hemispheres and across areas using ANOVA for the Auditory Naming and Reversed Speech conditions separately. The Greenhouse–Geisser correction to the degrees of freedom was used when Mauchly’s test of sphericity was significant. It is worth noting that at a macroscopic level, the structural differences between the brains of these anophthalmic subjects and controls were small (Bridge et al., 2009). The lack of structural differences between the two groups means that even though the function of the ‘visual’ areas is certainly not visual in the anophthalmia group, it is practical to use these functionally defined probabilistic maps to further examine the pattern of activity across the occipital cortex.

Resting-state functional MRI data were acquired in the five anophthalmic subjects, six of the sighted control subjects used in the task functional MRI and a further six sighted controls of the same age. For the resting-state scan, sighted subjects kept their eyes closed, and all were told to relax and do nothing for the duration of the scan. Whole-head $T_2^*$-weighted echo-planar images (echo time = 28 ms) were acquired every 2 s for 6 min (180 volumes). Each volume comprised 34 3.5 mm axial slices (in-plane resolution 3 × 3 mm). The echo-planar imaging data from each subject were preprocessed and registered with the same parameters as in the task functional MRI except that the high-pass temporal filter was changed to 150 s to remove frequencies <0.0067 Hz. The preprocessed data (180 volumes per subject) were temporally concatenated across all subjects (12 controls and five anophthalmic subjects) to produce a single 4D data set. Independent component analysis running in Melodic in FSL (Beckmann and Smith, 2004) was used to identify 25 components.

![Figure 1](https://academic.oup.com/brain/article-abstract/135/5/1566/307457/1568|Brain 2012: 135; 1566–1577 K. E. Watkins)

Figure 1. Regions of interest in occipital, temporal and frontal areas. Coloured areas are thresholded probabilistic maps. These are overlaid using FreeSurfer (Dale et al., 1999; Fischl et al., 1999) onto the inflated cortical surface of the left hemisphere of the average brain, which was generated from the six control and the five anophthalmic subjects in whom both task and the resting-state functional MRI data were obtained. IFG = inferior frontal gyrus; LOC = lateral occipital complex.
in the single 4D data set, which represented group-averaged networks of brain regions with temporally correlated activity. Two resting-state networks showing strongly lateralized patterns of activity that are almost left–right mirror images of each other were selected from these components for further analysis. These resting-state networks were previously described as ‘fronto-parietal’ and seen to correspond strongly to spatial components derived from the BrainMap database associated with cognitive and language tasks for the left-lateralized resting-state network and perception, somesthesia and pain for the right-lateralized resting-state network (Smith et al., 2009).

To compare the spatial extents of resting-state networks between the anophthalmic and the sighted groups, we employed a dual-regression approach (Filippini et al., 2009). The first stage of the dual regression regressed each of the group independent-component analysis spatial maps against each individual subject’s resting data set to extract a subject-specific time-course for each resting-state network. These time-courses were then regressed against the subject’s resting data set to extract subject-specific spatial maps. For each resting-state network, voxel-wise comparisons between the maps in anophthalmic and sighted subjects were made using a t-test and the significance of these statistics was evaluated using non-parametric permutation testing (5000 permutations) and threshold-free cluster enhancement (P < 0.05, corrected; Smith and Nichols, 2009). The resulting statistical spatial maps characterize the significant differences between the two groups in the resting-state networks.

To further investigate the pattern of lateralization for functional connectivity in the occipital cortex, we calculated the interhemispheric correlation of activity in the regions of interest representing visual areas V1, V2, V3, V4, V3A and lateral occipital complex; correlated activity from control areas in A1 and inferior frontal gyri were also compared. The time-series of BOLD activity in these areas was extracted for each region of interest in each hemisphere for each subject; the correlation coefficients for the time-series data extracted from homotopic pairs of regions of interest were calculated and compared between groups using non-parametric Mann–Whitney U tests, suitable for the low n and significantly different variances between groups.

Results

Task-related functional magnetic resonance imaging

Whole-brain analyses

Brain activation during Auditory Naming (compared with Rest) in both anophthalmic and sighted subjects was present in cortical regions typically associated with language processing: left posterior inferior frontal gyrus and anterior insula, left superior temporal sulcus, supplementary motor cortex extending to the anterior cingulate cortex bilaterally, left supramarginal and angular gyr, and the posterior ventral temporal cortex on the left extending to the ventral medial occipital cortex around the calcarine sulcus bilaterally (Fig. 3A). The activation in anophthalmic subjects also showed greater activity for Auditory Naming compared to Reversed speech in the left inferior frontal gyrus and posterior ventral temporal cortex bilaterally. The overall difference in the level of activation for this contrast might reflect the different numbers of subjects in the two groups. Even though the size of the group was small, the anophthalmic subjects showed additional activity in the lateral occipital cortex bilaterally and the left anterior temporal pole extending to the ventral surface (Fig. 3A). The lateral occipital areas were significantly more active for this contrast in anophthalmic subjects compared with controls, i.e. the interaction between group and condition was significant only in lateral occipital complex bilaterally (Fig. 3B and Table 1). There were no areas in which the controls showed significantly greater activity than the anophthalmic subjects for the Auditory Naming > Rest contrast.

Brain activation to Reversed Speech (compared with Rest) in the control group was limited to the superior temporal gyrus bilaterally. In anophthalmic subjects, however, it arose also in lateral occipital complex and V3A on the lateral surface extending to the medial dorsal occipital cortex bilaterally. The activity in the lateral regions in the left hemisphere and the medial regions bilaterally in anophthalmia was significantly greater than that of the control group (Z > 3.1, P < 0.05 cluster corrected; Table 1 and Supplementary Fig. 1). There were no areas where controls had significantly greater activity than anophthalmic subjects for the Reversed Speech > Rest contrast.

The data of individual subjects revealed that lateral occipital complex was activated (Z > 3.1, P < 0.05 cluster corrected) in both hemispheres in all anophthalmic subjects during Auditory Naming and additionally in the left hemisphere of one anophthalmic subject (Case 5) during Reversed Speech. During Auditory Naming, 1 of the 12 controls showed some activation in lateral occipital complex bilaterally and another one in right lateral occipital complex but none of them showed activation in lateral occipital complex for Reversed Speech. Area V3A on the left was activated in four of the five anophthalmic subjects during Auditory Naming and additionally during Reversed Speech in Case 5, who was the only subject that also showed activity in left lateral occipital complex during Reversed Speech.

The analysis of the Auditory Naming > Reversed Speech contrast in controls revealed activation of left inferior frontal gyrus extending to the dorsal premotor cortex, left anterior insula, left superior temporal sulcus, supplementary motor cortex extending to the anterior cingulate cortex bilaterally, left supramarginal and angular gyr, and the posterior ventral temporal cortex on the left extending to the ventral medial occipital cortex around the calcarine sulcus bilaterally (Fig. 3A). The activation in anophthalmic subjects also showed greater activity for Auditory Naming compared to Reversed speech in the left inferior frontal gyrus and posterior ventral temporal cortex bilaterally. The overall difference in the level of activation for this contrast might reflect the different numbers of subjects in the two groups. Even though the size of the group was small, the anophthalmic subjects showed additional activity in the lateral occipital cortex bilaterally and the left anterior temporal pole extending to the ventral surface (Fig. 3A). The lateral occipital areas were significantly more active for this contrast in anophthalmic subjects compared with controls, i.e. the interaction between group and condition was significant only in lateral occipital complex bilaterally (Fig. 3B and Table 1). There were no areas in which the controls showed significantly greater activity than the anophthalmic subjects for the Auditory Naming > Reversed Speech contrast.
Region-of-interest analyses

The percentage signal change during Auditory Naming and Reversed Speech was extracted in each hemisphere separately in each subject for visual areas (V1–V4, V3A and lateral occipital complex) and for the inferior frontal gyrus and A1 areas (Figs 1 and 4). Results for the two conditions were analysed in separate ANOVAs. We used three-way ANOVA (with factors of visual region-of-interest, hemisphere and group) for the visual areas, and separate two-way ANOVAs (with factors of hemisphere and group) for each of the inferior frontal gyrus and A1 regions-of-interest.

The anophthalmic subjects had significantly more activity than controls in the 'visual' regions-of-interest during Auditory Naming \[F(1,15) = 14.29, P = 0.002\] and Reversed Speech \[F(1,15) = 8.88, P = 0.009\]. The anophthalmic subjects, but not the sighted controls, also showed a significant leftward asymmetry in activation levels across visual areas during Auditory Naming [group × hemisphere interaction: \(F(1,15) = 21.00, P < 0.0005\)] and Reversed Speech [group × hemisphere interaction: \(F(1,15) = 6.93, P = 0.019\)]. The group × region-of-interest interaction was significant for Auditory Naming \([F(1.9, 29.2) = 5.76, P = 0.008]\), characterized by higher activity in V3A compared to V3 and V4 amongst the anophthalmics; this interaction was not significant in the analysis of data from the Reversed Speech condition. The main effect of region-of-interest was also significant for Auditory Naming \([F(1.9, 29.2) = 10.75, P < 0.0005]\) characterized by a pattern of higher activity in lateral occipital complex, V1 and V2 compared to V3 and V4 in both the anophthalmic and the sighted control subjects; it should be noted, however, that the levels of activity across all visual areas in the sighted controls were very low (Fig. 4).

In the whole-brain analysis contrast of Auditory Naming > Reversed Speech, the control but not anophthalmic group showed significantly greater activity in V1 (Fig. 3A). At the slightly higher threshold used for the contrasts between Auditory Naming and Rest and Reversed Speech and Rest, neither group showed significant V1 activity. The region-of-interest analysis reveals that in sighted controls, V1 is activated slightly above...
baseline (Rest) for Auditory Naming but not for Reversed Speech, whereas in anophthalmic subjects V1 is activated for both Auditory Naming and Reversed Speech to approximately equal levels and the difference between the activity levels is small. Therefore, both anophthalmic subjects and controls activate V1 during Auditory Naming but the anophthalmic subjects also activate V1 to the same extent when listening to Reversed Speech. The anophthalmic subjects and sighted controls both showed a significant leftwards asymmetry of activity in the inferior frontal gyrus \(r^{(1,15)} = 2.39, P < 0.05\) (corrected) threshold. Results for the basic contrasts with rest are reported used a \(Z > 3.1\) and \(P < 0.05\) (corrected) threshold.

The location of the highest peak in a cluster is given; selected sub-peaks within the large clusters are also described.

Results for the interaction of Group x Condition (anophthalmia versus controls: auditory naming > reversed speech) are reported for a mixed-effects analysis using a cluster-forming threshold of \(Z > 2.3\) and an extent threshold of \(P < 0.01\) (corrected). Results for the basic contrasts with rest are reported used a \(Z > 3.1\) and \(P < 0.05\) (corrected) threshold.

### Functional connectivity at rest

#### Whole-brain resting-state networks

Independent component analysis of the resting data across all subjects identified several resting-state networks showing brain regions with temporally correlated BOLD signal (Beckmann et al., 2006), two of which were lateralized. These networks generally only indicated positive correlations, even though there may also be regions of negative correlation (anti-correlated). The left-lateralized ‘language’ resting-state network comprised the inferior frontal gyrus, medial superior frontal cortex and inferior parietal cortex (angular gyrus). The same component in the anophthalmic group additionally included the left lateral occipital cortex and the right inferior frontal sulcus extending posteriorly to the right ventral premotor cortex (Fig. 5A). When the left-lateralized resting-state networks in the two groups were compared statistically, only the left lateral occipital cortex extending to the ventral surface showed significantly stronger functional connectivity with the remainder of the ‘language’ resting-state network in the anophthalmic group compared with controls (Fig. 5B). The right anterior calcarine cortex (V1) does not form part of the ‘language’ resting-state network in either group, but shows significantly greater negative correlation with components of this resting-state network in the anophthalmic subjects compared with controls (Fig. 5B).

The right-lateralized ‘perception’ resting-state network in the control group comprised lateral prefrontal, medial superior frontal, inferior parietal (supramarginal and angular gyri) and inferior temporal cortex. This resting-state network is also clear in the anophthalmic subjects and extends to the medial parietal and occipital cortex. The statistical comparison of the right-lateralized resting-state networks in the two groups showed significantly greater functional connectivity between the right lateral occipital cortex and the rest of the network in the anophthalmic subjects (Supplementary Fig. 2).

### Interhemispheric correlations in regions of interest

The interhemispheric correlations of the time-series data extracted from retinotopic visual areas (V1–V4, V3A), lateral occipital complex, primary auditory cortex (A1), and the inferior frontal gyrus were calculated for each subject. Figure 6 shows the mean correlation coefficients for control (red) and anophthalmic (blue)

---

**Table 1 Areas showing significant group differences in activation contrasts**

<table>
<thead>
<tr>
<th>Peak locations</th>
<th>Cluster size</th>
<th>Z-statistic</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anophthalmia &gt; Controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Auditory Naming &gt; Rest</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left lateral occipital cortex (V3A)</td>
<td>3829</td>
<td>5.58</td>
<td>-50</td>
<td>-82</td>
<td>2</td>
</tr>
<tr>
<td>Left dorsal occipital cortex</td>
<td>36</td>
<td>5.09</td>
<td>-20</td>
<td>-98</td>
<td>20</td>
</tr>
<tr>
<td>Left ventral occipito-temporal cortex</td>
<td>52</td>
<td>5.24</td>
<td>-36</td>
<td>-78</td>
<td>-22</td>
</tr>
<tr>
<td>Right lateral occipital cortex</td>
<td>1659</td>
<td>5.19</td>
<td>50</td>
<td>-76</td>
<td>-4</td>
</tr>
<tr>
<td>Right posterior fusiform gyrus</td>
<td>4.29</td>
<td>54</td>
<td>-68</td>
<td>-18</td>
<td></td>
</tr>
<tr>
<td>Left inferior temporo-occipital cortex</td>
<td>159</td>
<td>4.57</td>
<td>-42</td>
<td>-46</td>
<td>-32</td>
</tr>
<tr>
<td>Reversed Speech &gt; Rest</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right dorsal medial occipital cortex</td>
<td>1160</td>
<td>4.45</td>
<td>2</td>
<td>-82</td>
<td>26</td>
</tr>
<tr>
<td>Left dorsal medial occipital cortex</td>
<td>4.10</td>
<td>-10</td>
<td>-86</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Left dorsal occipital cortex (V3A)</td>
<td>4.10</td>
<td>-30</td>
<td>-82</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Left posterior parietal cortex</td>
<td>4.42</td>
<td>-18</td>
<td>-78</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Left lateral occipital cortex</td>
<td>332</td>
<td>4.22</td>
<td>-46</td>
<td>-74</td>
<td>-8</td>
</tr>
<tr>
<td>Left ventral occipito-temporal cortex</td>
<td>3.93</td>
<td>-36</td>
<td>-78</td>
<td>-22</td>
<td></td>
</tr>
<tr>
<td>Auditory Naming &gt; Reversed Speech&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left lateral occipital cortex</td>
<td>1026</td>
<td>4.70</td>
<td>-50</td>
<td>-82</td>
<td>2</td>
</tr>
<tr>
<td>Right lateral occipital cortex</td>
<td>3.38</td>
<td>-34</td>
<td>-90</td>
<td>-8</td>
<td></td>
</tr>
<tr>
<td>Right fusiform gyrus</td>
<td>4.09</td>
<td>52</td>
<td>-78</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Left inferior temporal cortex</td>
<td>3.25</td>
<td>50</td>
<td>-52</td>
<td>24</td>
<td></td>
</tr>
</tbody>
</table>

The location of the highest peak in a cluster is given; selected sub-peaks within the large clusters are also described.

<sup>a</sup>Results for the interaction of Group x Condition (anophthalmia versus controls: auditory naming > reversed speech) are reported for a mixed-effects analysis using a cluster-forming threshold of \(Z > 2.3\) and an extent threshold of \(P < 0.01\) (corrected). Results for the basic contrasts with rest are reported used a \(Z > 3.1\) and \(P < 0.05\) (corrected) threshold.
Figure 3  Brain activity during Auditory Naming compared to Reversed Speech. Group averages for control and anophthalmic subjects (A). Regions showing significantly greater activity in the five anophthalmic subjects than in the 12 sighted controls (B). Coloured areas represent significant differences in activity using a cluster-forming threshold of $Z > 2.3$ and a family wise error corrected significance threshold on the extent of $P < 0.01$. The colour bar shows the range of the $Z$-statistic (2.3–5.0) used for display of the statistical maps. Images were overlaid on the cortical surface as described in the legend to Fig. 1.

Figure 4  Region-of-interest analysis for the Auditory Naming (left) and Reversed Speech (right) conditions in the task functional MRI. Percentage signal change in BOLD signal relative to rest is plotted for visual areas (V1–V4, V3A and lateral occipital complex), primary auditory cortex (A1) and inferior frontal gyrus (IFG). Solid lines and filled circles = anophthalmia; dotted lines and open triangles = controls; red = left hemisphere, blue = right hemisphere. LOC = lateral occipital complex.
Previous studies suggested that primary sensory areas have higher interhemispheric correlation than regions later in the hierarchy of processing (Stark et al., 2008). Furthermore, it might be expected that an area such as the posterior inferior frontal gyrus would have relatively low interhemispheric correlation, because of hemispheric specialization for language processing.

Consistent with previous studies, V1 shows the highest correlation between hemispheres in resting activity in both control and anophthalmic subjects, and the difference between the groups is

Figure 5 Functional connectivity at rest. Left-lateralized ‘language’ resting state network in control and anophthalmic subjects (A). The network in the anophthalmic subjects includes regions of the occipital lobe. The statistical maps are overlaid using FreeSurfer (see legend to Fig. 1 for details). Significant differences between the left-lateralized networks in the two groups (B). The left lateral occipital cortex has significantly greater correlation with the rest of the ‘language’ network in the anophthalmic subjects compared to the sighted controls (yellow areas). The right anterior calcarine is significantly more negatively correlated with the rest of the ‘language’ network in the anophthalmic subjects compared to sighted controls (blue areas). The colour bar shows the $P$-value range used to display the significant differences in functional connectivity evaluated using permutation testing and threshold-free cluster enhancement ($P < 0.05$, corrected). Statistical maps were overlaid onto the MNI-152 template using FSLview.
Primary visual cortex in the sighted brain is located in the upper and lower banks of the calcarine sulcus. This cortical area (V1) in anophthalmia was active when any auditory stimulus was presented and did not differ according to its language content, that is, it was activated bilaterally by the auditory naming and the reversed speech conditions. This pattern of activation of visual areas during language processing in anophthalmia is consistent, therefore, with the known hierarchy of visual processing in sighted subjects. It contrasts with previous studies showing a reversal of the hierarchy of processing across occipital cortex for both language and memory tasks in the congenitally blind (Amedi et al., 2003) and significant activation to language stimuli but not reversed speech in V1 in the early blind (Bedny et al., 2011).

The role of ‘shape-selective’ cortical areas in language processing

Several previous studies of congenital, early and late blind subjects reported increased activity in extrastriate cortical areas during auditory processing. For example, sound imagery (De Volder et al., 2001), auditory motion (Lewis et al., 2010), sentence processing (Roder et al., 2002; Bedny et al., 2011), verb generation to heard nouns (Burton et al., 2002b; Amedi et al., 2003), phonological and semantic processing of word lists (Burton et al., 2003) and semantic decisions to heard nouns (Noppeney et al., 2003). In several of these studies, the activation was left-lateralized (Noppeney et al., 2003; Bedny et al., 2011). Consistent with our findings in the resting-state data, Noppeney et al. (2003) described the extrastriate cortex as coupling to the frontal-temporal ‘core’ semantic retrieval system. Similarly, Liu et al. (2007) found increased functional connectivity at rest between the occipital cortex and language areas in the frontal lobes of the early blind. Functional imaging and brain stimulation studies suggest that the response in occipital cortex to language stimuli reflects semantic rather than phonological processing (Burton et al., 2003; Amedi et al., 2004; Bedny et al., 2011). Whether these regions in anophthalmia contribute to phonological or semantic processing or to both cannot be settled with our current data. Further studies are required to examine the roles of the lateral occipital complex and V3A in different aspects of auditory and language processing in anophthalmia.

The auditory-naming functional task used here allowed the investigation of several language-specific processes (speech perception, comprehension, lexical search and retrieval) without movements produced by speaking and with minimal memory load. The task was easy and therefore, the functional activation in occipital areas does not reflect expertise. In a study of early and late blind subjects, Burton et al. (2002a, b) showed activity in this region for lexical retrieval from related words presented either aurally or via Braille, suggesting that this is a ‘language’ region rather than an auditory one. Our data are consistent with this interpretation as the lateral occipital complex was consistently activated in the auditory naming condition but only one anophthalmic subject showed activity in this region when listening to reversed speech. Anecdotally, it is noteworthy that this anophthalmic subject is employed as a sound engineer and it is possible that the lateral occipital complex activity might reflect his expert ability in attempting to extract speech information from the reversed speech condition. The use of a reversed speech control condition allowed us to examine language-specific activation and auditory activation separately. It should be noted, however, that these conditions differed in several respects, including the degree to which

not significant \( P = 0.064 \). Anophthalmic subjects have a similar correlation level to control subjects in the two control areas, A1 and inferior frontal gyrus, outside of the occipital lobe (Fig. 6). In extrastriate ‘visual’ areas, however, there is significantly less correlation between the two hemispheres in the anophthalmic subjects compared to the controls \( P < 0.05 \); indeed, the correlation levels in these higher-order ‘visual’ areas are comparable in strength to those in the inferior frontal gyrus.

![Figure 6](https://example.com/figure6.png)

**Figure 6** Interhemispheric correlation of BOLD signals at rest in homotopic regions of interest. Sighted controls = blue; anophthalmic subjects = red. All extrastriate ‘visual’ areas (V2–V4, V3A and lateral occipital complex) have significantly lower correlation in anophthalmic compared to sighted control subjects \( P < 0.05 \). Mean interhemispheric correlation coefficients are plotted. Error bars represent standard error of the mean. IFG = inferior frontal gyrus; LOC = lateral occipital complex.
attention is engaged, and this in turn might vary between controls and anophthalmic subjects. We might also speculate that the activity seen in all anophthalmic subjects in the lateral occipital complex evoked by a task requiring search and retrieval of lexical items involves accessing representations of objects or mental imagery. These cannot be visual representations but they might be tactile; previous studies in sighted controls revealed activation in the lateral occipital complex to tactile but not auditory processing of objects (Amedi et al., 2002) and to tactile shape-coded sounds (Kim and Zatorre, 2011). However, such representations and imagery are presumably also available to the sighted controls yet they did not activate these regions during the same task.

The left and right fronto-parietal resting-state networks compared in anophthalmia and sighted controls are reliably seen in healthy adult control brains (Beckmann et al., 2005; Damoiseaux et al., 2006). Networks with similar spatial distributions corresponded to functional task performance in the BrainMap database in the cognition-language domain for the left-lateralized resting-state network and perception–somesthesia–pain domain for the right-lateralized resting-state network (Smith et al., 2009). These two left–right mirrored resting-state networks are also present in the brains of term and preterm infants (Doria et al., 2010) and, interestingly, include the lateral occipital cortex at this early stage of development. This observation suggests that structural and functional connectivity exists early in development between occipital and the fronto-parietal areas, and is subsequently lost during later maturational processes when visual inputs to the region dominate. When these are absent, as in the anophthalmic subjects, connectivity is maintained and possibly strengthened.

The primary visual cortex is not specialized for language in anophthalmia

Activation of striate cortex (V1) in blind subjects is frequently but inconsistently reported. For Braille reading, at least, it seems to depend on the age of onset of blindness and the degree to which the task engages semantic processing and requires prior visual experience to aid visual imagery (Buchel et al., 1998; Burton et al., 2002a). For auditory tasks, several studies report activity in V1 in the blind as for extrastriate areas described above. Interference by brain stimulation applied over the occipital pole in blind—but not sighted subjects—disrupts accuracy on a verb generation task resulting primarily in semantic rather than phonological or articulatory errors (Amedi et al., 2004).

In our study, the region-of-interest analysis of ‘visual’ areas revealed that both controls and anophthalmic subjects showed activity in V1 during auditory naming that was not evident at the statistical threshold used in the whole-brain analysis. The anophthalmic subjects additionally showed activity in V1 during listening to reversed speech, whereas controls did not. Therefore, in the whole-brain contrast between auditory naming and reversed speech, the controls show greater activity than anophthalmics around the calcarine sulcus. This interaction between group and condition reflects the lack of activation of visual areas while listening to reversed speech in controls rather than reduced activation during auditory naming in anophthalmics. The fact that the anophthalmics activate V1 during both task conditions involving auditory processing is consistent with a subcortical pattern of reorganization dependent on auditory inputs from the thalamus.

Consistent with the task functional MRI data, extrastriate areas showed increased functional connectivity with language areas at rest while ‘V1’ was not recruited to these networks. Interhemispheric activity at rest between homotopic occipital regions was significantly correlated in both anophthalmic and sighted control subjects. As shown previously (Stark et al., 2008), this was highest in V1 in the controls. Spontaneous resting activity in V1 is likely to be highly synchronous and well correlated between hemispheres as each receives inputs corresponding to separate halves of the same visual field. Lower interhemispheric coordination is thought to reflect a more independent mode of operating in homotopic regions. The anophthalmic subjects showed the same degree of highly correlated interhemispheric activity as controls in both primary sensory cortices tested (V1 and A1) and in the inferior frontal gyrus, though the correlation in this heteromodal association area was lower in both groups. The fact that V1 has a very high interhemispheric correlation of spontaneous resting activity in anophthalmia and that this does not differ from that seen in sighted controls is consistent with the assertion that V1 maintains its position early in the hierarchy of processing in the occipital cortex in anophthalmia. In contrast, the interhemispheric correlation of spontaneous resting activity in higher-order ‘visual’ areas (V3, V4, V3A and lateral occipital complex) was significantly reduced in anophthalmia to the level seen in heteromodal cortex, such as the inferior frontal gyrus. The reduction relative to the correlation present in sighted controls might reflect different roles for these cortical regions in the anophthalmic brain and potentially their recruitment into brain networks supporting lateralized functions such as language and attention.

Why does the pattern of functional organization in anophthalmia differ from that in other blind populations?

The function of the occipital lobe and the ‘visual system’ in general in blind subjects may depend on several factors. A major difference between populations that are clinically anophthalmic and those that are congenital or early blind is the total absence of any visual experience even antenatally. We should be cautious in interpreting differences between populations based on separate studies that employed different tasks and different analysis techniques. One advantage of our study is the homogeneity of the anophthalmic subjects, in which we can be certain of no light perception. Nevertheless, the number of individuals available to study remains small and makes generalization to a wider population difficult. Many of the congenitally or early blind subjects studied have suffered retinopathy of prematurity, where the eyes and retinas are present and functional in utero but are damaged by blood vessel growth and retinal detachment at some point after birth. In these subjects, the visual system will have received some light stimulation and this may play a role in determining the later function of their ‘visual’ areas. A similar
pattern of limited light stimulation or even spontaneous retinal activity is present in other types of early or congenital blindness (e.g. Leber congenital amaurosis). Subjects with retinopathy of prematurity and Leber amaurosis would form ideal groups in which to compare the patterns of functional organization with those in anophthalmia and allow the investigation of the effects of very early exposure to light on this organization.

The notion that the reorganization of function in anophthalmia might differ from that in other congenitally blind individuals is supported by data obtained in the blind mole rat (Bronchti et al., 2002) and mutant anophthalmic mice (2DRDCT/An; Chabot et al., 2007, 2008). Both these rodent models of blindness, which result from limited or absent development of the eye, retina and optic nerve, show auditory inputs to the dorsal lateral geniculate nucleus from the inferior colliculus, with consequential auditory activation of ‘visual’ cortex. In contrast, ophthalmic mice that were bilaterally enucleated post-natally have reduced volume of the dorsal lateral geniculate nucleus relative to the mutant anophthalmic mouse (Cullen and Kaiserman-Abramof, 1976), which was attributed to the degeneration of their geniculostral projections. Anophthalmic mice also show auditory-driven c-Fos labelling in the dorsal lateral geniculate nucleus and V1 cortex, whereas in post-natally enucleated mice, no auditory inputs to or activation of these structures were present (Chabot et al., 2007). On the other hand, the post-natally enucleated mice showed stronger auditory activity in V2, which abuts auditory cortex in the mouse brain (Chabot et al., 2007).

Conclusion

Our study demonstrates that anophthalmia is associated with recruitment of cortical areas in the visual processing hierarchy normally specialized for shape processing. The adaptation may rely on the persistence and strengthening of neonatal inputs from the auditory system to these visual areas (Innocenti and Clarke, 1984; Falchier et al., 2002; Rockland and Ojima, 2003). These connections may have avoided normal developmental cell death (apoptosis), proliferated or become strengthened as a result of the absence of competition from any visual inputs or increased dependence on intact sensory processing. However, any such cortical plasticity has not resulted in any major structural changes observable with MRI as evidenced by our previous structural imaging study in the same anophthalmic subjects (Bridge et al., 2009), which revealed no significant differences in the volume of the cortical visual areas that showed increased functional activity here. In contrast, areas in the inferior frontal gyrus and ventral precentral sulcus showed increased grey matter bilaterally in the anophthalmic subjects and reduced functional activation during language processing compared to the sighted controls. The current data raise the possibility that the calcarine region in anophthalmic subjects receives abnormal thalamic input, as suggested by studies in anophthalmic mice (Chabot et al., 2007, 2008). Further investigation of both connectivity and function of the medial and lateral geniculate nuclei is required to establish the exact nature of this input and the processing of visual areas in anophthalmia.

Acknowledgements

We wish to thank our participants for their contributions to this research. We also wish to thank Dr. Ned Jenkinson and Dr. Ione Fine for helpful comments on the manuscript.

Funding

The Medical Research Council (G971/397B to A.C.); the Royal Society (University Research Fellowship UF0760314 to H.B.); the Leverhulme Trust (Emeritus Fellowship EM/2EM/2010/00 to A.C.); the EPA Cephalosporin Trust (to I.A.); and the Academy of Medical Sciences/The Health Foundation (Senior Surgical Scientist Award to N.R.).

Supplementary material

Supplementary material is available at Brain online.

References


