Visual experience shapes functional connectivity between occipital and non-visual networks

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Abstract

Comparisons across adults with different sensory histories (blind vs. sighted) have uncovered effects of experience on human brain function. In people born blind visual cortices are responsive to non-visual tasks and show altered functional connectivity at rest. Since almost all research has been done with adults, little is known about the developmental origins of this plasticity. Are infant visual cortices initially functionally similar to those of sighted adults but blindness then causes reorganization? Alternatively, do infants start more similar to blind adults, with vision required to set up the sighted pattern?

To distinguish between these possibilities, we compare resting state functional connectivity across blind (n = 30) and blindfolded sighted (n = 50) adults to a large cohort of sighted infants (Developing Human Connectome Project, n = 475).

In sighted adults, visual cortices show stronger functional coupling with nonvisual sensory-motor networks (i.e., auditory, somatosensory/motor) than with higher-cognitive prefrontal cortices. By contrast in blind adults, visual cortices show stronger coupling with higher-order prefrontal cortices. Remarkably, we find that infant secondary visual cortices functionally resemble those of blind more than sighted adults, consistent with the idea that visual experience is required to set up long-range functional connectivity. Primary visual cortices show a mixture of instructive effects of vision and reorganizing effects of blindness. Finally, only congenitally blind adults show biased lateralization of fronto-occipital connectivity, whereas infants and sighted adults show no such bias. Recruitment of occipital networks for lateralized cognitive functions in blindness, such as language, may cause lateralization of connectivity.

These results reveal instructive and reorganizing effect of experience on human brain function.

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Abbreviations: dHCP = Developing Human Connectome Project; MT = middle temporal; LO = lateral occipital complex; V1 = primary visual cortex; SD = standard deviation; fMRI = functional MRI; ROI = regions of interest; BOLD = blood oxygen level-dependent; CSF = spinal fluid; WM = white matter; PCA = principal components analysis; ICA = independent component analysis; S1/M1 = primary somatosensory and motor cortex; A1 = primary auditory cortex; PFC = prefrontal cortices; OC = occipital cortices; MTH = math-responsive region; LG = language-responsive region; EF = executive function-responsive (response-conflict) region.

Introduction

Studies of vision loss provide insight into how early life experience shapes cortical function and behavior. Visual cortices of adults born blind show enhanced responses during non-visual tasks, such as Braille reading by touch, spoken language comprehension and auditory spatial processing.[1–9] Occipital cortices of blind adults also show distinctive patterns of spontaneous neural activity and functional connectivity (resting state correlations) with non-visual networks.[1,10–16] The developmental origins of these function differences across blind and sighted people are not known, since almost all research is done with adults.

One possibility is that at birth infants start out with in the 'prepared' sighted adult state and differences among sighted and blind adults reflects reorganization caused by blindness. However, it is also possible that some of the functional differences observed between blind and sighted adults reflect the lack of *instructive* effects of visual experience. In other words, infants start out similar to blind adults and vision 'instructs' the sighted adult pattern. To distinguish between these possibilities, we compare the functional connectivity profile of visual cortices of blind and sighted adults to a large cohort of sighted infants on average 2-weeks old (Developing Human Connectome Project, dHCP). Resting state data provide a common measure of cortical function across these diverse populations.

To our knowledge no prior study has directly compared resting functional connectivity in infants to adult populations with different sensory histories. Previous resting state studies comparing sighted infants and adults have largely reported similarities across ages.[17–22] However, these prior studies focused mostly on connectivity *within* large scale functional networks (e.g., visual areas are more correlated with other visual areas than with somatosensory networks), whereas differences between blind and sighted adults are observed in connectivity *between* the visual system and non-visual functional networks i.e., which non-visual networks are most correlated with the visual system?

We examined the connectivity profile of three secondary visual areas on the lateral, dorsal and ventral occipital surface that have previously been found to respond to different non-visual tasks in blind adults and show different functional connectivity across blind and sighted adults.[4–6] In blind adults, these three regions respond to different higher-cognitive tasks, including language, numerical reasoning and executive control.[4–6] The precise function of these regions in sighted people is not known. Roughly, they correspond to the anatomical location of areas such as motion area V5/MT+, the lateral occipital complex (LO), V3a and V4v.[23,24] Together, these three regions tile the majority of lateral occipital cortex, providing a good sample of the connectivity profile of higher-order visual areas. We also examined connectivity of primary visual cortex (V1), which likewise shows altered task-based responses and functional connectivity in congenitally blind adults.[1,6,8,9,11,12,15,25,26] Since many previous studies have found that blindness alters the balance of connectivity between visual cortex and higher-order prefrontal as opposed to sensory-motor regions, this was our primary outcome measure. We also examined changes in connectivity lateralization – i.e., the balance of between vs. within hemisphere connectivity.

To preview the results, we find that the functional connectivity of secondary visual areas in infants resembles that of blind more than sighted adults, whereas V1 of infants falls between the two adult populations. This suggests that vision plays an instructive role in setting up the balance of connectivity between visual cortex and non-visual networks. In contrast, lateralization patterns appear to reflect blindness-related reorganization.

Materials and methods

Participants

Fifty sighted adults and thirty congenitally blind adults contributed the resting state data (sighted n = 50; 30 females; mean age = 35.33 years, standard deviation (SD) = 14.65; mean years of education = 17.08, SD = 3.1; blind n = 30; 19 females; mean age = 44.23 years, SD = 16.41; mean years of education = 17.08, SD = 2.11; blind vs. sighted age, $t_{(78)} = 2.512$, $p < 0.05$; blind vs. sighted years of education, $t_{(78)} = 0.05$, $p = 0.996$). Blind and sighted participants had no known cognitive or neurological disabilities (screened through self-report). All adult anatomical images were read by a board-certified radiologist and no gross neurological abnormalities were found. All the blind participants had at most minimal light perception from birth. Blindness was caused by pathology anterior to the optic chiasm (i.e., not due to brain damage). All participants gave written informed consent under a protocol approved by the Institutional Review Board of Johns Hopkins University.

Neonate data were from the third release of the Developing Human Connectome Project (dHCP) (n = 783) (https ://www.developing connectome.org). Ethical approval was obtained from the UK Health Research Authority (Research Ethics Committee reference number: 14/LO/1169). After quality control procedures (described below), 475 subjects were included in data analysis, with one scan per subject. The average age from birth at scan = 2.79 weeks (SD = 3.77); average gestational age at scan = 41.23 weeks (SD = 1.77). We only included infants who were full-term or scanned at term-equivalent age if preterm, while not being flagged by the dHCP project team as not passing quality control for functional MRI (fMRI) images (n = 634). Infants with more than 160 motion outliers were exclude (n = 116 dropped). Motion-outlier volumes were defined as DVARS (the root mean square intensity difference between successive volumes) higher than 1.5 interquartile range above the 75th centile, after motion and distortion correction. Infants with signal drop-out in regions of interest (ROI) were

also excluded (n = 43 dropped). To identify signal dropout, we first averaged blood oxygen level-dependent (BOLD) signal intensity for all time point, for each subject, in each of 100 parcel defined by Schaefer's atlas.[27] For each ROI (n = 18 ROIs) in the current study, signal dropout was then identified as BOLD intensity lower than -3 standard deviations, where the Mean and standard deviations were identified across all 100 cortical parcels. Participants were excluded if any of the ROIs showed a signal dropout.

Image acquisition

Blind and sighted adult MRI anatomical and functional images were collected on a 3T Phillips scanner at the F. M. Kirby Research Center. T1-weighted anatomical images were collected using a magnetization-prepared rapid gradient-echo (MP-RAGE) in 150 axial slices with 1 mm isotropic voxels. Resting state fMRI data were collected in 36 sequential ascending axial slices for 8 minutes. TR = 2 s, TE = 0.03 s, flip angle = 70°, voxel size = 2.4 × 2.4 × 2.5 mm, inter-slice gap = 0.5 mm, field of view (FOV) = 192 × 172.8 × 107.5. Participants completed 1 to 4 scans of 240 volume each (average scan time = 710.4 second per person). During the resting state scan, participants were instructed to relax but remain awake. Sighted participants wore light-excluding blindfolds to equalize the light conditions across the groups during the scans.

Infants (dHCP) Anatomical and functional images were collected on a 3T Phillips scanner at the Evelina Newborn Imaging Centre, St Thomas' Hospital, London, UK. A dedicated neonatal imaging 219 system including a neonatal 32-channel phased-array head coil was used. T2w multi-slice fast spin-echo images were acquired with in-plane resolution 0.8x0.8mm^2 and 1.6mm slices overlapped by 0.8mm (TR = 12000 ms, TE = 156 ms, SENSE factor 2.11 axial and 2.6 sagittal). In infants, T2w images were used as the anatomical image because the brain anatomy is more clearly in T2w than in T1w images. Fifteen minutes of resting state fMRI data were collected using a used multiband 9x accelerated echo-planar imaging (TR = 392 ms, TE = 38ms, 2300 volumes, with an acquired resolution of 2.15 mm isotropic). Single-band reference scans were acquired with bandwidth-matched readout, along with additional spin-echo acquisitions with both AP/PA fold-over encoding directions.

Data analysis

Resting state data were preprocessed using FSL version 5.0.9,[28] DPABI version 6.1,[29] FreeSurfer,[30] and in-house code (https://github.com/NPDL/Resting-state_dHCP). The functional data for all groups were linearly detrended and low-pass filtered (0.08 Hz).

For adults, functional images were registered to the T1-weighted structural images, motion corrected using MCFLIRT,[31] and temporally high-pass filtering (150 s). No subject had excessive head movement (> 2mm) or rotation (> 2°) at any timepoint. Resting state data are known to include artifacts related to physiological fluctuations such as cardiac pulsations and respiratory-induced modulation of the main magnetic field. A component-based method, CompCor,[32] was therefore used to control for these artifacts. Particularly, following the procedure described in Whitfield-Gabrieli *et al*.[33] nuisance signals were extracted from 2-voxel eroded masks of spinal fluid (CSF) and white matter (WM), and the first 5 principal components analysis (PCA) components derived from these signals was regressed out from the processed BOLD time series. In addition, a scrubbing procedure was applied to further reduce the effect of motion on functional connectivity measures.[34,35] Frames with root mean square intensity difference exceeding 1.5 interquartile range above the 75th centile, after motion and distortion correction, were censored as outliers.

The infants resting state functional data were pre-processed by the dHCP group using the project's in-house pipeline.[36] This pipeline uses a spatial independent component analysis (ICA) denoising step to minimize artifact due to multi-band artefact, residual head-movement, arteries, sagittal sinus, CSF pulsation. For infants, ICA denoising is preferable to using CSF/WM regressors. because it is challenging to accurately define anatomical boundaries of CSF/WM due to the low imaging resolution comparing with the brain size and the severe partial-volume effect in the neonate.[36] Like in the adults, frames with root mean square intensity difference exceeding 1.5 interquartile range above the 75th centile, after motion and distortion correction, were considered as motion outliers. Out from the 2300 frames, a subset of continuous 1600 with minimum number of motion outliers was kept for each subject. Motion outliers were censored from the subset of continuous 1600, and a subject was excluded from further analyses when the number of outlier exceeded 160 (10% of the continues subset).[37]

For both groups of adult and infants, we performed a temporal low-pass filter (0.08 Hz low-pass cutoff) and a linear detrending. ROI-to-ROI connectivity was calculated using Pearson's correlation between ROI-averaged BOLD timeseries (ROI definition see below). The All *t*-

tests and *F*-tests are two-sided. The comparison of correlation coefficients was done using cocor software package and Pearson and Filon's z.[38,39]

ROI definition

ROIs in the frontal and occipital cortices were defined from separate task-based fMRI experiments with blind and sighted adults.[4–6] Three separate experiments were conducted with the same group of blind and sighted subjects (sighted n=18; blind n=23). The language ROIs in the occipital and frontal cortices were identified by sentence > nonwords contrast in an auditory language comprehension task.[6] The math ROIs were identified by math > sentence contrast in an auditory task where participants judged equivalence of pairs of math equations and pairs of sentences.[5] The executive function ROIs were identified by no-go > frequent go contrast in an auditory go/no-go task with non-verbal sounds.[4] The occipital ROIs were defined based on group comparisons blind > sighted in a whole-cortex analysis. For example, the occipital language ROI were defined as the cluster that responded more to auditory sentence than auditory nonwords conditions in blind, relative to sighted, in a whole-cortex analysis. All three occipital ROIs were defined in the right hemisphere. Left-hemisphere occipital ROIs were created by flipping the right-hemisphere ROIs to the left hemisphere. The frontal ROIs were defined based on a whole-cortex analysis which combined all blind and sighted adult data. For example, the frontal language ROI was defined as responded more auditory sentence than auditory nonwords conditions across all blind and sighted subjects, constrained to the prefrontal cortex. For frontal ROIs, the language ROI was defined in the left, and the math and executive function ROI were defined in the right hemisphere, then flip to the other hemisphere. See Supplementary Fig. 1 for the full views of ROIs in right hemisphere.

The V1 was defined from a previously published anatomical surface-based atlas (PALS-B12).[40] The primary somatosensory and motor cortex (S1/M1) ROI was selected as the area that responds more to the go than no-go trials in the auditory go/no-go task across both blind and sighted groups, constrained to the hand area in S1/M1 search-space from neurosynth.org (term “hand movements”).[4] The primary auditory cortex (A1) ROI was defined as the transverse temporal portion of a gyral-based atlas.[41,42]

All the ROIs were defined in standard space. For infants, the ROIs were subsequently transformed into each subject’s native space using a two-step approach. First, the ROIs were converted from the adult's MNI space into the 40-week dHCP template.[43] ANTS, previously

shown to be effective in pediatric studies,[44–47] was utilized to estimate the deformation field between these two spaces. In this step, the infant's scalp and cerebellum were masked, as these structures in the infant brain greatly differ from those in the adult and can introduce bias into the registration process, as outlined in a study by Cabral *et al.*[45] Secondly, the ROIs were further transformed from the 40-week space into individual's native spaces, employing the deformation field provided by the dHCP group. Nearest neighbor interpolation was applied in both steps (see examples of ROI in individual infant brains in the Supplementary Fig. 2). For adults, the ROIs were also transformed into each subject's native space, employing the deformation field estimated by FreeSurfer. For both adults and infants, any overlapping voxels between ROIs were removed and not counted toward any ROIs.

Data availability

Neonate data were from the second and third release of the Developing Human Connectome Project (https://www.developing connectome.org). The de-identified blind and sighted adults' data will be posted on Vivli.org upon publication of the current manuscript.

Results

The connectivity pattern of secondary visual areas depends on early visual experience

The connectivity profile of secondary visual cortex in sighted infants was more similar to that of blind than sighted adults.

Secondary visual areas of sighted adults showed stronger functional connectivity with non-visual sensory areas (primary somatosensory and motor cortex, S1/M1, and primary auditory cortex, A1) than with prefrontal cortices (PFC). By contrast, in blind adults, visual cortices showed higher functional connectivity with PFC than with non-visual sensory areas (S1/M1 and A1) (group (sighted adults, blind adults) by ROI (PFC, non-visual sensory) interaction effect: $F_{(1, 78)} = 148.819$, $p < 0.001$; post-hoc Bonferroni-corrected paired *t*-test, sighted adults: non-visual sensory > PFC: $t_{(49)} = 9.722$, $p < 0.001$; blind adults: non-visual sensory < PFC: $t_{(29)} = 8.852$, $p < 0.001$; Fig. 1).

Like in blind adults, in sighted infants, secondary visual cortices showed higher connectivity to PFC than non-visual sensory areas (S1/M1 and A1) (non-visual sensory < PFC paired *t*-test, $t_{(474)} = 20.144$, $p < 0.001$) (Fig. 1). The connectivity matrix of sighted infants was also more correlated with that of blind than sighted adults, but strongly correlated with both adult groups (secondary visual, PFC and non-visual sensory areas: sighted infants correlated to blind adults: $r = 0.721$, $p < 0.001$; to sighted adults: $r = 0.524$, $p < 0.001$; difference between correlations of infants to blind vs. to sighted adults: $z = 3.77$, $p < 0.001$; see Supplementary Fig. 3 for the connectivity matrices).

These results suggests that vision sets up the sighted functional connectivity pattern, i.e., enhances visual cortex connectivity to non-visual sensory-motor networks and dampens connectivity to higher-cognitive prefrontal networks.

We checked the robustness of these results in a number of ways. First, since blind participants were on average older, we performed analyses in an age-matched subgroups of sighted controls ($n = 29$) and found similar results to the full sample (see Supplementary Fig. 4). Next, we compared the effects across the three different secondary visual regions and found that the same pattern held across all three regions (Supplementary results and Supplementary Fig. 5). Finally, to check the robustness of the findings in infants we randomly split the infant dataset into two halves and did split-half cross-validation. Across all comparisons the results of the two halves were highly similar, suggesting the effects are robust (see Supplementary Fig. 6). We performed this validation procedure for all analyses reported below with similar results.

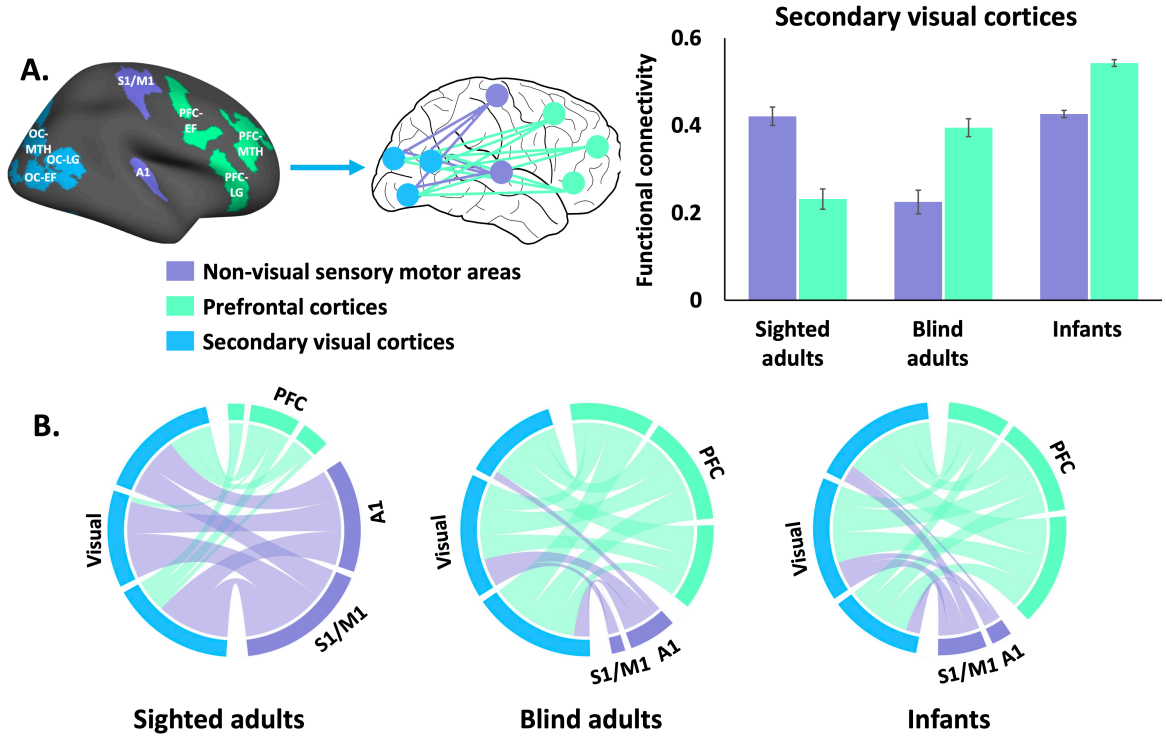

Figure 1 Functional connectivity of secondary visual cortices. (A) Bar graph shows functional connectivity (*r*) of secondary visual cortices (blue) to non-visual sensory motor areas (purple) and prefrontal cortices (green), averaged across occipital, PFC and sensory-motor ROIs (A1 and S1/M1) in sighted adults, blind adults and sighted infants. Regions of interest (ROI) displayed on the left. **(B)** Circle plots represent the connectivity of secondary visual cortices to non-visual networks, min-max normalized to [0,1], i.e., as a proportion. OC: occipital cortices; MTH: math-responsive region; LG: language-responsive region; EF: executive function-responsive (response-conflict) region.

The connectivity pattern of V1 influenced both by early visual experience and blindness

Next, we examined the functional connectivity of the primary visual cortex (V1) with non-visual sensory areas (S1/M1 and A1) and PFC. V1 showed the same dissociation between sighted and blind adults as secondary visual areas: in sighted adults, V1 has stronger functional connectivity with non-visual sensory areas than with PFC. By contrast, in blind adults, V1 shows stronger connectivity with PFC than with non-visual sensory areas (group (sighted adults, blind adults) by ROI (PFC, non-visual sensory) interaction: $F_{(1, 78)} = 125.775$, $p < 0.001$; post-hoc Bonferroni-corrected paired *t*-test, sighted adults non-visual sensory > PFC: $t_{(49)} = 9.404$, $p < 0.001$; blind adults non-visual sensory < PFC: $t_{(29)} = 7.128$, $p < 0.001$; Fig. 2; also

see Supplementary Fig. 7 for age-matched subgroups of sighted adults results and Supplementary Fig. 8 for infants split-half cross-validation results).

The pattern for sighted infants in V1 fell between that of sighted and blind adults. The connectivity matrix of sighted infants (V1, PFC, and non-visual sensory) was equally correlated with blind and sighted adults (infants correlated to blind adults: $r = 0.654$, $p < 0.001$; to sighted adults: $r = 0.594$, $p < 0.001$; correlation of infants with blind vs. with sighted adults: z = 0.832, $p = 0.406$; see Supplementary Fig. 3 for the connectivity matrices). The difference in connectivity strength between V1 to PFC and V1 to non-visual sensory regions was weaker in sighted infants than in sighted or blind adults (group (sighted adults, infants) by ROI (PFC, non-visual sensory) interaction effect: $F_{(1, 523)} = 92.21$, $p < 0.001$; group (blind adults, infants) by ROI (PFC, non-visual sensory) interaction effect: $F_{(1, 503)} = 57.444$, $p < 0.001$). V1 of sighted infants showed marginally stronger connectivity to non-visual sensory regions (S1/M1 and A1) than PFC (non-visual sensory regions > PFC, paired *t*-test, $t_{(474)} = 1.95$, $p = 0.052$; Fig. 2).

The dHCP cohort included both full-term neonates and preterm infants, scanned at their equivalent gestational age. Visual exposure therefore varied somewhat in duration across infants (from 0 to 19.71 weeks), with slightly longer exposure in preterm babies. This variation did not affect connectivity patterns either in V1 or secondary visual cortices (V1: $r = 0.06$, $p = 0.192$; secondary visual: $r = 0.004$, $p = 0.923$; see Supplementary Fig. 9). A few weeks of vision after birth is therefore insufficient to influence connectivity.

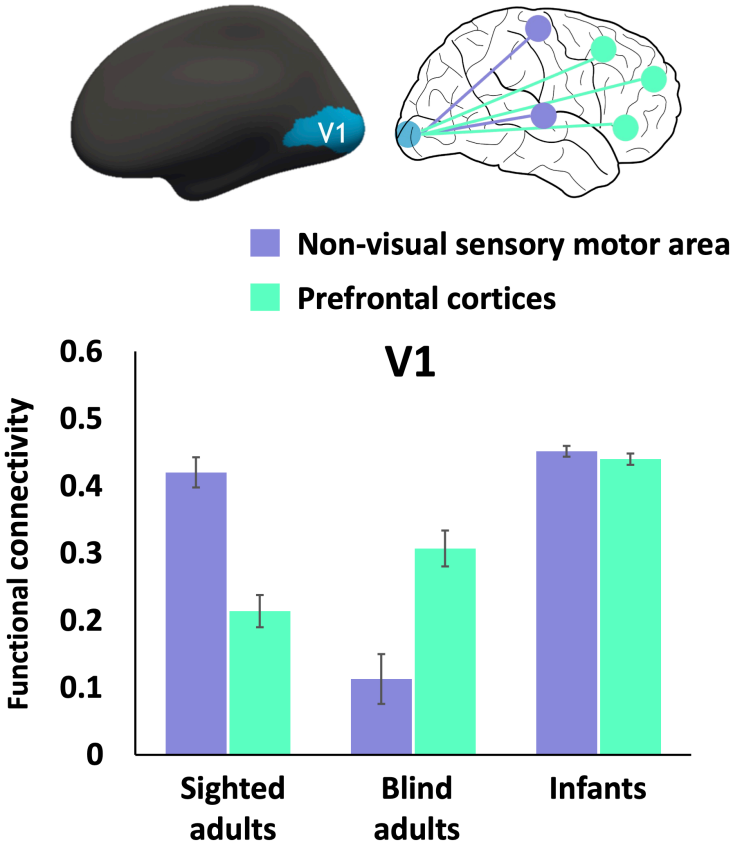

Figure 2 Functional connectivity of primary visual cortices (V1). Regions of interest (ROI) displayed on the upper. Bar graph shows functional connectivity (*r*) of V1 to non-visual sensory motor areas (purple) and prefrontal cortices (green), averaged across three PFC ROIs and sensory-motor ROIs (S1/M1 and A1).

Blindness enhances lateralization of connectivity between visual cortex and non-visual networks

Next, we examined the patterns of connectivity lateralization. Previous studies find that task-based cross-modal responses in visual cortices are lateralized in blind adults and co-lateralize with fronto-parietal networks with related functions.[4,48] For example, language-responsive occipital areas collateralize with language responsive prefrontal areas across individuals.[48]

Consistent with these task-based connectivity patterns, we found that relative to sighted adults, blind adults showed a stronger dominance of within hemisphere connectivity between secondary and primary visual cortices and PFC. That is, in people born blind, left visual networks are more strongly connected to left PFC networks, whereas right visual networks are more strongly connected to right PFC. By contrast, there is no hemispheric bias in the sighted

group (group (blind adults, sighted adults) by lateralization (within hemisphere, between hemisphere) interaction, secondary visual cortices: $F_{(1,\ 78)} = 131.51$, $p < 0.001$; post-hoc Bonferroni-corrected paired: *t*-test: sighted adults within hemisphere > across hemisphere: $t_{(49)} = 5.778$, $p < 0.001$; blind adults within hemisphere > across hemisphere: $t_{(29)} = 10.735$, $p < 0.001$; V1: $F_{(1,\ 78)} = 87.211$, $p < 0.001$; post-hoc Bonferroni-corrected paired: *t*-test: sighted adults within hemisphere > between hemisphere: $t_{(49)} = 3.251$, $p = 0.101$; blind adults within hemisphere > between hemisphere: $t_{(29)} = 7.019$, $p < 0.001$).

With respect to laterality, sighted infants resembled sighted more than blind adults (Fig. 3; also see Supplementary Fig. 10 for age-matched subgroups of sighted adults results and Supplementary Fig. 11 for infants split-half cross-validation results), suggesting that these adult-group differences in laterality reflect blindness-driven reorganization. There was a significant difference in laterality between blind adults and sighted infants (group (blind adults, infants) by lateralization (within hemisphere, between hemisphere) interaction effect: $F_{(1,\ 503)} = 303.04$, $p < 0.001$). There was no difference between sighted adults and sighted infants (group (sighted adults, infants) by lateralization (within hemisphere, across hemisphere) interaction effect: $F_{(1,\ 523)} = 2.244$, $p = 0.135$; see supplementary results for a detailed group comparison of within and across hemisphere differences). Similar group by laterality interaction pattern are also observed in V1 (group (blind adults, infants) by lateralization (within hemisphere, between hemisphere) interaction effect: $F_{(1,\ 503)} = 123.608$, $p < 0.001$; group (sighted adults, infants) by lateralization (within hemisphere, across hemisphere) interaction effect: $F_{(1,\ 523)} = 2.827$, $p = 0.093$). The incorporation of visual cortices into lateralized functional networks (e.g., language, response selection) in blindness may drive stronger within-hemisphere connectivity in this population.[4,48,49]

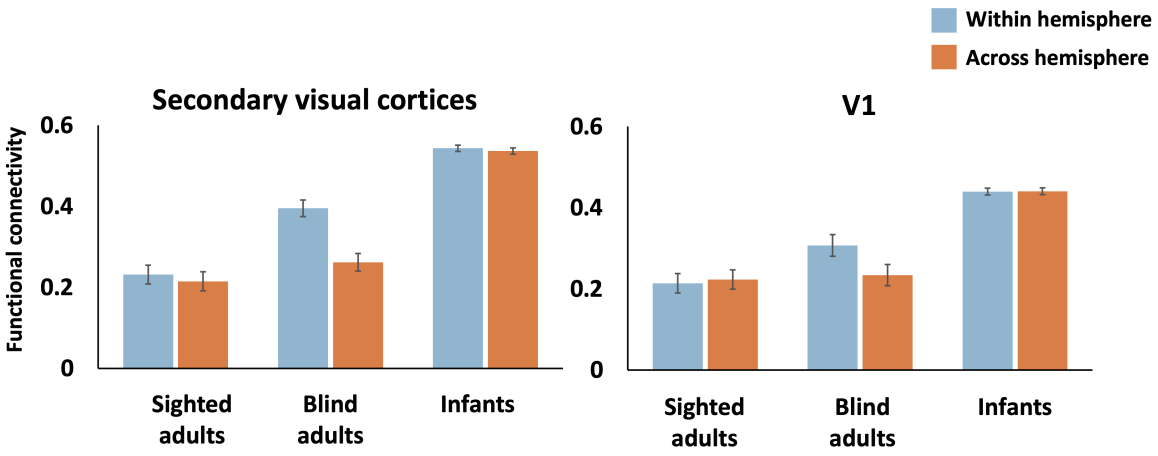

Figure 3 Within hemisphere vs. across hemisphere functional connectivity. Bar graph shows within hemisphere (blue) and across hemisphere (orange) functional connectivity (*r* coefficient of resting state correlations) of secondary visual (left) and V1 (right) to prefrontal cortices in sighted adults, blind adults, and sighted infants. Blind adults show a larger difference than any of the other groups.

Immature fronto-occipital connectivity specialization at birth

Within prefrontal and occipital cortices, resting state connectivity patterns are specialized and aligned with the functional specialization in task-based data.[1,4,5] For example, language-responsive subregions of occipital cortex show strongest functional connectivity with language-responsive sub-regions of PFC, whereas math-responsive occipital areas show stronger connectivity with math-responsive PFC (Fig. 4).[1,4–6] Is this fronto-occipital connectivity specialization present in infancy, potentially driving task-based cross-modal specialization?

We compared connectivity preferences across three prefrontal and three occipital regions previous shown to activate preferentially in language (sentences > math), math (math > sentences) and response-conflict (no-go > go with tones) tasks respectively.[4–6] For ease of viewing, Fig. 4 shows results from two of the three regions, math and language. However, all statistical analyses included all three areas (See Supplementary Fig. 12 for all three regions; also see Supplementary Fig. 13 for age-matched subgroups of sighted adults results and Supplementary Fig. 14 infants split-half cross-validation results).

Sighted infants showed a less differentiated fronto-occipital connectivity pattern relative to sighted and blind adults (Group (sighted adults, blind adults, sighted infants) by occipital regions (math, language, response-conflict) by PFC regions (math, language, response-

conflict) interaction $F_{(8, 2208)} = 16.323$, $p < 0.001$). Unlike in adults, in infants, all the occipital regions showed stronger correlations with math- and response-conflict related prefrontal areas than language-responsive prefrontal areas (Fig. 4 and Supplementary Fig. 12, also see supplementary Fig. 15 for connectivity matrix.). The occipital region that is sensitive to response-conflict in blind adults showed equivalent correlations with math and response-conflict PFC regions in infants. The region of occipital cortex that responds to language and shows the strongest connectivity with language responsive PFC in blind adults, showed stronger connectivity with math and response-conflict PFC areas in infants.

Although fronto-occipital connectivity was not adult-like in infants, biases in infants we somewhat consistent with future differentiation: the preferential correlation with math responsive PFC was strongest in those occipital areas that go on to develop math responses in blind adults (occipital regions (math, language, response-conflict) by PFC regions (math, language, response-conflict) interaction in infants $F_{(4, 1896)} = 85.145$, $p < 0.001$, post-hoc Bonferroni-corrected paired *t*-test see Supplementary Table 1). Although the occipital region that is language-responsive in blind adults actually showed stronger connectivity to math and response-conflict areas of PFC in infants, this preference was smaller than the other two occipital ROIs examined, perhaps providing a less strong intrinsic bias to overcome.

Note that these findings regarding regional specialization need to be interpreted with caution because of potential anatomical alignment issues between adult and infant brains for these more fine-grained comparisons. In other words, lack of specialization in infants could reflect the different location of the areas in this population. Furthermore, we do not know whether the language/number/executive function distinctions exist in prefrontal cortices of infants. However, prior evidence suggests that at least some of the prefrontal specialization present in adults is already present even in young babies and connectivity could in principle precede task-based specialization.[50]

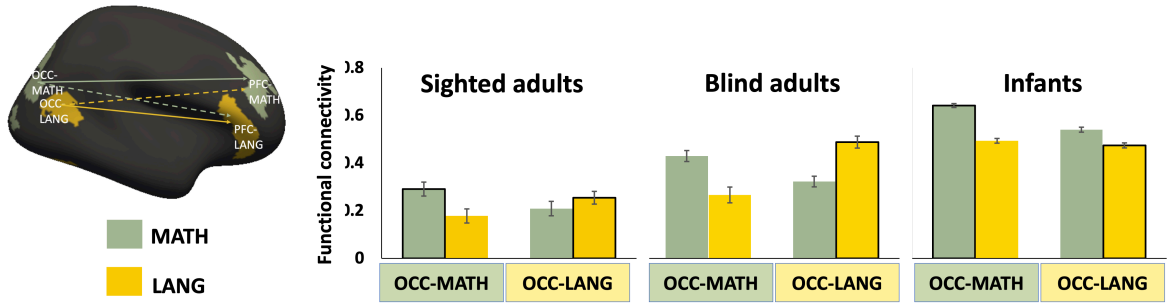

Figure 4 Occipito-frontal functional connectivity. Bar graph shows across functional connectivity of different sub-regions of prefrontal (PFC) and occipital cortex (OCC) in sighted adults, blind adults, and sighted infants. Sub-regions (regions of interest) were defined based on task-based responses in a separate dataset of sighted (frontal) and blind (frontal and occipital) adults.[4–6] PFC/OCC-MATH: math-responsive regions were more active when solving math equations than comprehending sentences. PFC/OC-LANG: language-responsive regions were more active when comprehending sentences than solving math equations [4–6]. In blind adults these regions show biases in connectivity related to their function i.e., language-responsive PFC is more correlated with language responsive OCC. No such pattern is observed in infants.

Discussion

We find evidence for instructive effects of visual experience in setting up the functional connectivity between human visual cortices and non-visual networks. The sighted adult functional connectivity pattern, although the most common in the population, is not the 'default' starting state but rather requires visual experience to establish. This was particularly evident in the case of secondary visual cortices, where, resting state connectivity patterns with non-visual networks in sighted infants resemble those of blind adults more so than those of sighted adults. Both in infants and blind adults, secondary occipital areas showed stronger functional connectivity with higher-order prefrontal cortices than with other sensory-motor networks (S1/M1, A1). Consistent with this observation, one previous study with a small sample of infants found strong connectivity between lateral occipital and prefrontal areas [17]. In V1, infants fell somewhere in between sighted and blind adults, suggesting an effect both of vision and of blindness on connectivity. We hypothesize that vision as well as temporally coordinated multi-modal experiences contribute to establishing the sighted connectivity profile.

A key question concerns the behavioral relevance of these connectivity signatures for vision and multimodal integration, since visual behavior is likely to be influenced by the

communication of visual cortices with non-visual networks. An increasing number of people who grew up blind will have the possibility of sight restoration in adulthood e.g., through cataract removal, corneal transplant or gene therapy. Recent evidence suggests that sight recovery individuals show some multimodal integration deficits.[51–54] There is also evidence that occipital oscillations, which affect cross-network communication, are different in this population.[55] It will therefore be important to determine the contribution of connectivity to visual and multimodal sensory behavior and how connectivity might be shaped later in life.

For people who remain blind throughout life, the infant connectivity profile could play a role in enabling recruitment of visual cortices by non-visual functions such as language and non-verbal executive processes. This recruitment could then itself influence both task-based recruitment and functional connectivity.

The clearest evidence for blindness-related reorganization in the current study was observed in the case of laterality, where sighted infants resemble sighted adults in both V1 and secondary visual cortices. Relative to the other two groups, people who are born blind show more lateralized connectivity patterns between occipital and prefrontal cortices. Previous studies suggest that in people born blind occipital and non-occipital language responses are co-lateralized.[48] We speculate that habitual activation of visual cortices by higher-order tasks, which are themselves highly within individual (e.g., language), contributes to this shift in blindness.

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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