Title: Instructive and reorganizing effects of experience on development of human visual cortices

Mengyu Tian[1,2], Xiang Xiao[3], Huiqing Hu[4], Rhodri Cusack[4], Marina Bedny[1]

[1] Department of Psychological and Brain Sciences, Johns Hopkins University, Baltimore, Maryland 21218

[2] Center for Educational Science and Technology, Beijing Normal University, Zhuhai 519087, China

[3] Neuroimaging Research Branch, National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD 21224, USA

[4] Trinity College Institute of Neuroscience and School of Psychology, Trinity College Dublin, Dublin 2, Ireland

Abstract

Visual behavior and visual cortex function in adulthood are affected by early visual experience. In humans, the developmental origins of these differences amongst adults are not known. It is often assumed that differences reflect reorganizing effects of blindness on cortical function. Whether vision also plays an instructive role is not known. Here we compare newly available resting state (functional connectivity) data from two large cohorts of sighted infants (Developing Human Connectome Project (dHCP), second release: n=327, third release： n=475) to data from sighted adults (blindfolded, n=50) and blind adults (n=30). By comparing the "starting state" of infants to that of blind and sighted adults, we dissociate the instructive contributions of visual experience from the reorganizing effects of blindness on functional connectivity of visual cortices. As previously reported, we find that in sighted adults, visual networks show stronger functional connectivity with other sensory-motor networks (i.e., auditory, somatosensory) than with higher-cognitive prefrontal networks. Adults born blind show the opposite pattern: stronger functional connectivity between visual and prefrontal than visual and other non-visual sensory-motor networks. The resting state patterns of infants resemble those of blind adults in secondary visual cortices, revealing an instructive role of vision in establishing the sighted adult connectivity pattern. In primary visual cortex (V1), the sighted infants show an intermediate pattern between that of sighted and blind adults, suggesting both instructive effects of vision and reorganizing effects of blindness in V1. Relative to both adult groups, when comparing connectivity across different sub-regions of visual and prefrontal cortex, infants show less specialization relative to both adult groups. Finally, lateralization of connectivity in infants resembles that of sighted adults, consistent with reorganizing effects of blindness. These results dissociate instructive and reorganizing effect of experience on visual cortex functional connectivity, providing insight into developmental mechanisms.

Introduction

Studies of visual development provide a model for understanding how early life experience shapes cortical function and behavior (Hensch, 2005; Hubel & Wiesel, 1970; Sadato et al., 1996). Research in visually deprived animals has identified both instructive and reorganizing effects of early life experience on cortical function (Espinosa & Stryker, 2012; Molnár et al., 2020; Reh et al., 2020). An example of reorganization comes from studies of ocular dominance columns in V1. Columnar organization is present from birth in most mammals but can be disrupted by imbalanced visual input from the two eyes early in life (Crair et al., 1998; Espinosa & Stryker, 2012; Horton & Hocking, 1996; Hubel & Wiesel, 1970; Katz & Crowley, 2002; Sengpiel & Kind, 2002). On the other hand, instructive effects of visual experience are observed in the case of direction selectivity in early visual cortices of ferrets. Direction selectivity is weak or absent at birth and requires visual motion experience to emerge (Li et al., 2006; Rochefort et al., 2011). In humans, visual cortex function and behavior differs in adulthood in cases of atypical early visual experience. However, instructive, and reorganizing effects on cortical function have not been dissociated, since until recently it has not been possible to measure cortical function in human infants.

Adults who had dense cataracts as infants show lower visual acuity, altered face and object recognition and multimodal integration (Badde et al., 2020; Guerreiro et al., 2015; Le Grand et al., 2001; Maurer et al., 2007; McKyton et al., 2015; Röder & Kekunnaya, 2021). Visual cortices of individuals born blind show enhanced 'cross-modal' responses during auditory and tactile tasks, such as Braille reading, spoken language comprehension, auditory spatial attention and auditory response selection (Bedny et al., 2011; Burton et al., 2012; Collignon et al., 2011; Kanjlia et al., 2021, 2021; Masuda et al., 2021; Sadato et al., 1996).

Differences in task-based responses across blind and sighted adults are accompanied by differences in spontaneous neural activity at rest i.e., differences in functional connectivity or resting state correlations (e.g. Liu et al., 2007). Resting state correlations have been widely used to identify functional networks across populations and are known to be constrained by anatomical connectivity and influenced by experience (Biswal et al., 1995; Lewis et al., 2009; Stevens et al., 2010).

Adults born blind show enhanced resting state correlations (relative to the sighted) between visual and prefrontal networks, especially those with analogous functions (Bedny et al., 2011; Burton et al., 2014; Liu et al., 2007; Striem-Amit et al., 2015; Watkins et al., 2012). For example, 'visual' areas that respond to spoken language and Braille in blind adults show enhanced functional connectivity with prefrontal language regions at rest, while those active during arithmetic tasks are more correlated with math-responsive prefrontal areas (PFC) (Abboud & Cohen, 2019; Bedny et al., 2011; Kanjlia et al., 2016, 2021). Interestingly, at rest, visual cortices of people born blind show *reduced* correlations with non-visual early sensory motor areas (i.e., auditory cortex A1, sensory-motor cortex S1/M1) (Bedny et al., 2011; Burton et al., 2014; Liu et al., 2007; Yu et al., 2008). This is even though during cross-modal tasks (e.g., auditory localization), visual areas of blind adults are more active and more correlated with these same non-visual sensory-motor areas (Collignon et al., 2011; Klinge et al., 2010).

In sum, in resting state data, visual cortices of sighted adults show stronger coupling with other non-visual sensory-motor networks, by contrast, in blind adults, this pattern is reversed and coupling is stronger with prefrontal cortices.

The developmental origins of cortical function differences across visual cortices of blind and sighted adults are not known. Since the vast majority of humans use vision, it is often assumed that population differences are driven by blindness related reorganization and the sighted adult pattern is the 'default' starting state. However, it is also possible that some of the population differences reflect lack of instructive effects of visual experience, i.e., infants start out as blind adults and vision gives rise to the sighted adult pattern. A potentially informative and previously unexplored approach that we take in the current study is to compare visual cortices of blind and sighted adults to that of sighted infants. To do so, we use resting state data, which provide a common measure across these diverse populations. We leverage previously documented functional connectivity differences between blind and sighted adults together with newly publicly available large resting state datasets from sighted infants (Developing Human Connectome Project (dHCP) dataset, second release: n=327, third release： n=475). With these data, we ask: Does blindness 'reorganize' resting state connectivity patterns that are common to sighted infants and sighted adults? Alternatively, do some of the differences between sighted and blind adults reflect an instructive role of vision in establishing connectivity patterns?

To our knowledge no prior study has directly compared resting state organization in infants to adult populations with different sensory histories. Previous resting state studies comparing sighted infants to sighted adults have largely reported similarities across groups, consistent with the idea that any differences between blind and sighted adults are due to blindness-driven reorganization (Doria et al., 2010; Fransson et al., 2009; Gao et al., 2009; W. C. Liu et al., 2008; Zhang et al., 2019). However, these prior studies have focused on connectivity *within* large scale functional networks (e.g., visual areas are more correlated with other visual areas than with somatosensory networks). Within network connectivity is arguably heavily constrained by large scale anatomical tracts and therefore unlikely to be influenced by experience. Differences between blind and sighted adults are observed in connectivity *between* the visual system and different non-visual functional networks i.e., which non-visual networks are most correlated with the visual system?

To preview the results, we find evidence for both instructive contribution of vision and reorganizing effects of blindness on visual system connectivity. Moreover, the effects of experience differ systematically across the visual hierarchy with more evidence for instructive effects of vision in higher-order visual areas than V1.

Results & Discussion

Secondary visual areas of sighted adults showed stronger functional connectivity with non-visual sensory areas (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: $t_{(29)} = 8.852$, $p < 0.001$; Figure 1).

The connectivity profile of secondary visual cortex in sighted infants was more similar to that of blind than sighted adults, providing evidence for instructive effects of vision. In both samples of sighted infants, the secondary visual cortices showed higher connectivity to PFC than non-visual sensory areas (S1/M1 and A1) (non-visual sensory < PFC paired *t*-test in sighted infants, second release: $t_{(326)} = 13.224$, $p < 0.001$; third release: $t_{(474)} = 20.144$, $p <$

0.001) (Figure 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: infants correlated to blind adults: second release $r = 0.663$, $p < 0.001$; third release $r = 0.721$, $p < 0.001$; to sighted adults: second release $r = 0.516$, $p < 0.001$; third release $r = 0.524$, $p < 0.001$; difference between correlations of infants to blind vs. sighted adults: second release: z = 2.78, $p < 0.01$; third release: z = 3.77, $p < 0.001$; the comparison of correlation coefficients was done using cocor software package and Pearson and Filon's z (Diedenhofen & Musch, 2015; Pearson & Filon, 1898). see supplementary materials Figure S1 for the connectivity matrices) . This result suggests that visual experience enhances visual cortex connectivity at rest to non-visual sensory-motor networks and dampens connectivity to higher-cognitive prefrontal networks.

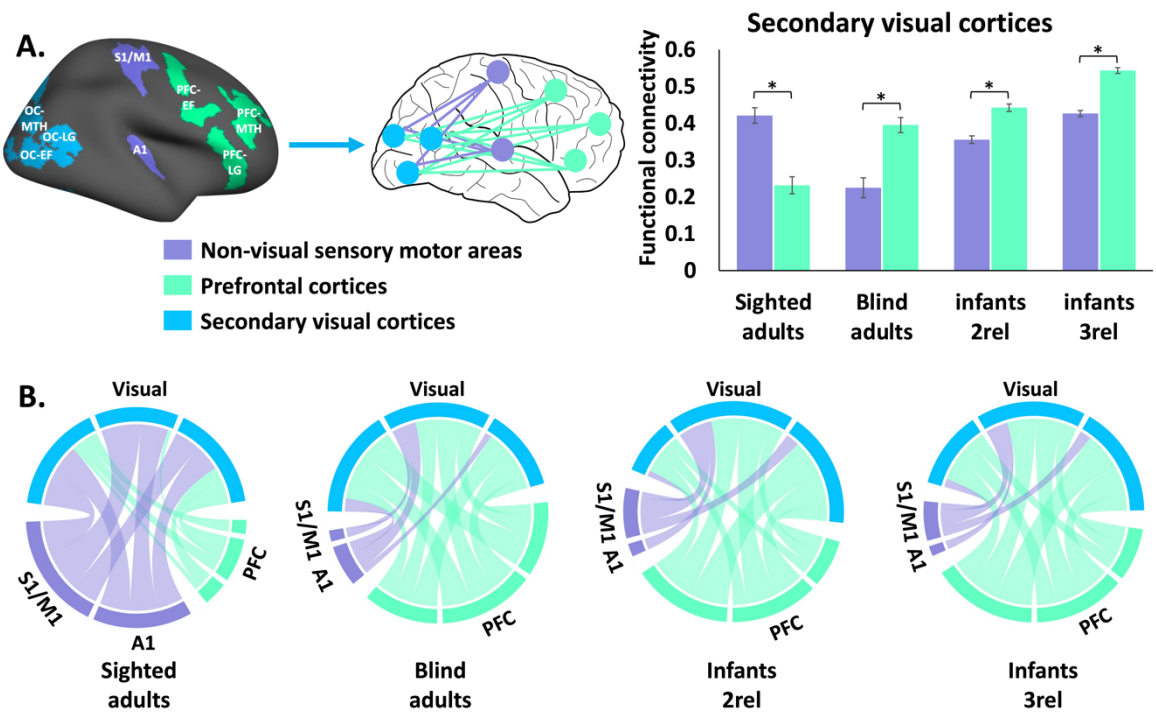

Figure 1 Functional connectivity of secondary visual cortices (blue) to non-visual sensory-motor networks (purple) and prefrontal cortices (green) in sighted adults, blind adults and two cohorts of sighted infants (2nd and 3rd release of dHCP). (A) Bar graph shows functional connectivity (r) of secondary visual cortices to non-visual sensory motor (purple) and PFC (green regions), averaged across occipital, PFC and sensory-motor ROIs (A1 and S1/M1). Regions of interest displayed on the left. (B) Circle plots show connectivity of secondary visual cortices to non-visual networks min-max normalized to [0,1] i.e., as a proportion. PFC: prefrontal cortices; OC: occipital cortices; MTH: math-responsive region; LG: language-responsive region; EF: executive function-responsive (response-conflict) region. Asterisks (*) denote significant Bonferroni-corrected pairwise comparisons ($p < 0.05$)

Next, we examined the functional connectivity of the primary visual cortex (V1) with non-visual sensory areas (S1/M1 and primary auditory cortex, 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 (S1/M1 and primary auditory cortex, A1) than with PFC. By contrast, in blind adults, V1 shows stronger connectivity with PFC than 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: $t_{(29)} = 7.128$, $p < 0.001$; Figure 2).

For V1, the pattern for sighted infants fell between that of sighted and blind adults. The connectivity matrix of the sighted infants (V1, PFC, and non-visual sensory) was equally correlated with blind and sighted adults (infants correlated to blind adults: second release $r = 0.613$, $p < 0.001$; third release $r = 0.654$, $p < 0.001$; to sighted adults: second release $r = 0.640$, $p < 0.001$; third release $r = 0.594$, $p < 0.001$; correlation of infants with blind vs. with Sighted: second release: $z = 0.375$, $p = 0.707$; third release: $z = 0.832$, $p = 0.406$; see supplementary material Figure S1 for the connectivity matrices). V1 of infants showed significantly stronger connectivity to non-visual sensory regions (A1 and S1/M1) than PFC in the second release and marginally stronger connectivity in the third release (non-visual sensory regions > PFC, paired *t*-test in sighted infants, second release: $t_{(326)} = 6.814$, $p < 0.001$; third release: $t_{(474)} = 1.95$, $p = 0.052$; Figure 2). The difference in connectivity strength between PFC and 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: second release: $F_{(1, 375)} = 57.376$, $p < 0.001$; third release: $F_{(1, 523)} = 92.21$, $p < 0.001$; group (blind adults, infants) by ROI (PFC, non-visual sensory) interaction effect: second release: $F_{(1, 355)} = 81.632$, $p < 0.001$; third release: $F_{(1, 503)} = 57.444$, $p < 0.001$). See supplementary results for A1 and S1/M1 connectivity separately.

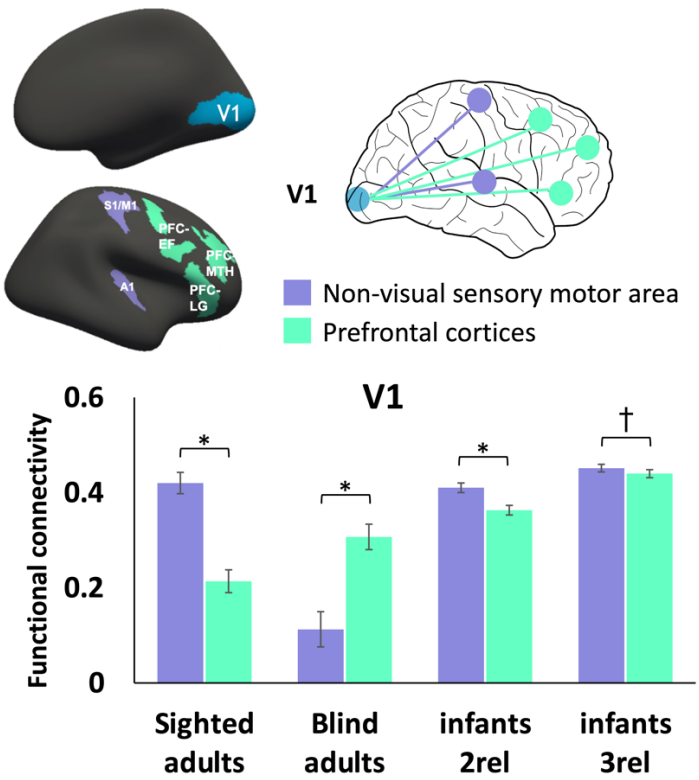

Figure 2 Functional connectivity of primary visual cortices (V1) to non-visual sensory-motor networks (purple) and prefrontal cortices (green) in sighted adults, blind adults, and two cohorts of sighted infants (2nd and 3rd release of dHCP). Regions of interest are shown in upper left. PFC: prefrontal cortices; MTH: math-responsive region; LG: language-responsive region; EF: executive function (response-conflict) region. Asterisks (*) denote significant Bonferroni-corrected pairwise comparisons ($p < 0.05$), Cross (†) denote marginal difference ($0.05 < p < 0.1$).

Next, we examined the developmental mechanism of lateralization differences across blind and sighted adults. Relative to sighted adults, secondary visual cortices of blind adults show a stronger dominance of within hemisphere connectivity. That is, left secondary visual networks are more strongly connected to left PFC networks, whereas right secondary visual networks are more strongly connected to right PFC (group (blind adults, sighted adults) by lateralization (within hemisphere, between hemisphere) interaction effect: $F_{(1, 78)} = 131.51$, $p < 0.001$; post-hoc Bonferroni-corrected paired: *t*-test: sighted adults within hemisphere > between hemisphere: $t_{(49)} = 5.778$, $p < 0.001$; blind adults within hemisphere > between hemisphere: $t_{(29)} = 10.735$, $p < 0.001$). Similar pattern were observed in primary visual cortex that blind adults show a stronger dominance of within hemisphere connectivity but there is no difference between the within and across hemisphere connectivity for sighted adults (group (blind adults, sighted adults) by ROI (within hemisphere, between hemisphere) interaction effect: $F_{(1, 78)} = 87.211$, $p < 0.001$; 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: $t_{(29)} = 7.019$, $p < 0.001$)(also see Kanjlia et al., 2021; Lane et al., 2017).

The present evidence from sighted infants suggests that these adult-group differences in laterality reflect blindness-driven reorganization: Sighted infants resembled sighted adults more so than blind adults (Figure 3). There was a significant difference in laterality between blind adults and sighted infants (group (blind adults, infants) by ROI (within hemisphere, between hemisphere) interaction effect: second release: $F_{(1, 355)} = 338.252$, $p < 0.001$; third release: $F_{(1, 503)} = 303.04$, $p < 0.001$). There was no difference between sighted adults and sighted infants (group (sighted adults, infants) by ROI (within hemisphere, across hemisphere) interaction effect: second release: $F_{(1, 375)} = 1.356$, $p = 0.245$; third release: $F_{(1, 523)} = 2.244$, $p = 0.135$; 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 ROI (within hemisphere, between hemisphere) interaction effect: second release: $F_{(1, 355)} = 99.026$, $p < 0.001$; third release: $F_{(1, 503)} = 123.608$, $p < 0.001$; group (sighted adults, infants) by ROI (within hemisphere, across hemisphere) interaction effect: second release: $F_{(1, 375)} = 5.486$, $p < 0.05$; third release: $F_{(1, 523)} = 2.827$, $p = 0.093$). 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 (Kanjlia et al., 2021; Lane et al., 2017; Tian et al., 2022).

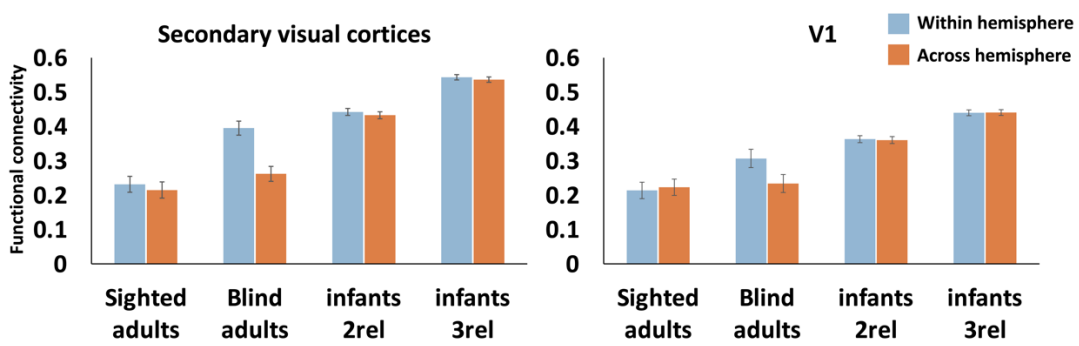

Figure 3 Within hemisphere (blue) vs. between hemisphere (orange) functional connectivity (r coefficient of resting state correlations) of secondary visual (left) and V1 (right) to prefrontal cortices in sighted adults, blind adults, and two cohorts of sighted infants (2nd and 3rd release of dHCP). Blind adults show a larger difference than any of the other groups.

Finally, we asked whether resting state patterns at birth could predict which prefrontal areas become coupled with which occipital regions, within hemisphere. In blind adults, resting state connectivity biases across different PFC areas align with specialization of task-based cross-modal responses within visual cortices (Abboud & Cohen, 2019; Amedi et al., 2003; Kanjlia et al., 2016, 2021). 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 (Bedny et al., 2011; Kanjlia et al., 2016). Does the fronto-occipital functional connectivity specialization observed in adults exist in infancy and potentially drive task-based cross-modal specialization? We compared connectivity of three prefrontal and three occipital regions which were found to respond to language, arithmetic and response-conflict in previous cohorts of sighted (frontal) and blind (occipital and frontal) adults (Kanjlia et al., 2016, 2021; Lane et al., 2015).

Contrary to the hypothesis that fronto-occipital functional connectivity specialization is adult-like from birth, both cohorts of sighted infants showed a less differentiated fronto-occipital connectivity pattern relative to sighted and blind adults. 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 (Figure 4; occipital regions (math, language, response-conflict) by PFC regions (math, language, response-conflict) interaction: infants second release: $F_{(4, 1304)} = 66.404$, $p < 0.001$; infants third release: $F_{(4, 1896)} = 85.145$, $p < 0.001$, post-hoc Bonferroni-corrected paired *t*-test see Supplementary Table S1). 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 occipito-frontal connectivity was not adult-like in infants, biases in infants may relate to 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. 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.

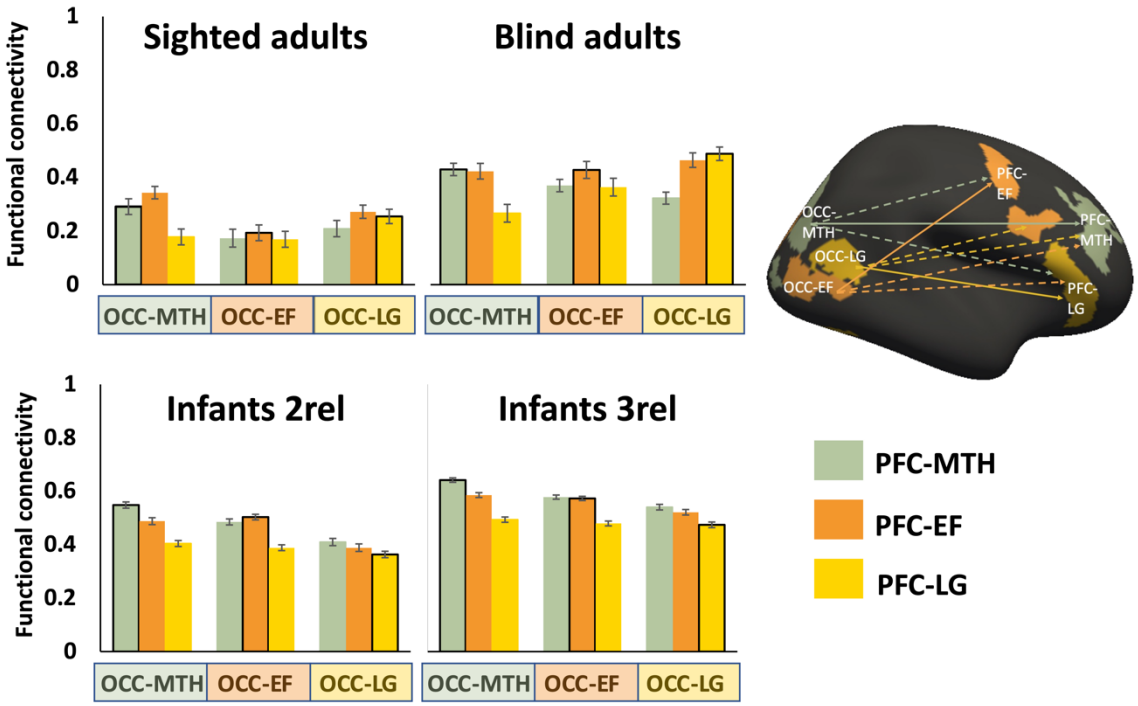

Figure 4 Occipito-frontal functional connectivity across different sub-regions of prefrontal (PFC) and occipital cortex (OCC) in sighted adults, blind adults, and two cohorts of sighted infants. Sub-regions (regions of interest) were defined based on task-based responses in a separate dataset of sighted (frontal) and blind (frontal and occipital) adults (Kanjlia et al., 2016, 2021; Lane et al., 2015). PFC/OC-MTH math-responsive regions were more active when solving math equations than comprehending sentences. PFC/OC-LG language-responsive regions were more active when comprehending sentences than solving math equations; EF: executive function (response-conflict) regions were more active during response inhibition (no-go) trials than active go trials during an auditory no-go task (Kanjlia et al., 2016, 2021; Lane et al., 2015). In blind adults (top right) 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. See supplementary material Figure S2 for connectivity matrix.

In sum, a comparison of resting state patterns in sighted infants, congenitally blind adults and sighted adults provides evidence both for instructive effects of visual experience and reorganizing effects of blindness on the development of functional connectivity in visual cortices. Interestingly, we observed differences across the cortical hierarchy. The instructive effects of visual experience were most clearly observed in secondary visual areas, where, resting state connectivity patterns with non-visual networks in sighted infants resemble those of blind adults more so than those of sighted adults. Vision appears to dampen functional connectivity of secondary visual cortices with prefrontal networks and enhance connectivity to non-visual sensory motor areas (i.e., A1 and S1/M1), possibly through synchronous multi-modal experiences. In this respect, the sighted adult pattern, although the most common in the population, is not the 'default' starting state but rather requires visual experience to establish. In V1, the infants start at an intermediate point between sighted and blind adults. There is a weak bias towards stronger connectivity with non-visual sensory-motor networks which is strengthened by vision and reversed by blindness. The clearest example of blindness-related change was observed in the case of laterality of connectivity between

occipital and prefrontal cortices, where sighted infants clearly resemble sighted adults. This suggests that strong lateralization of occipito-frontal connectivity is driven by blindness.

A key question for future research concerns the behavioral relevance of the observed connectivity patterns. 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 e.g., high correlations between occipital and prefrontal networks might contribute to enabling responses of visual cortices to spoken and written language in congenitally blind adults. Conversely, in people who grew up blind but whose vision is restored in adulthood e.g., through cataract removal or gene therapy, it will be important to determine the behavioral consequence of maintaining elements of the infant connectivity profile for visual perception and multi-modal integration, since some evidence suggests that (Ashtari, 2020)

Method

Participants

Fifty sighted controls and thirty congenitally blind individuals contributed the resting-state data (sighted N = 50; 30 females; age: M = 35.33, SD = 14.65; years of education: M = 17.08, SD = 3.1; blind N = 30; 19 females; age: M = 44.23, SD = 16.41; years of education: M = 17.08, SD = 2.11; blind vs. sighted age, $t_{(78)} = 2.512$, $p < 0.05$; blind vs. sighted years of education, $t_{(78)} = 0.05$, $p = 0.996$). Since blind participants were on average older, we also performed analyses in an age-matched subgroups of sighted controls and found similar results to the full sample (see Supplementary materials, Figure S3 to Figure S6). 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 second and third release of the Developing Human Connectome Project (dHCP) (https ://www.developing connectome.org). The Ethical approval was obtained from the UK Health Research Authority (Research Ethics Committee reference number: 14/LO/1169). The second release originally available data consists of images of 505 neonatal subjects and the third release consists of images of 783 neonatal subjects.
After quality control procedures (described below), 327 subjects in second release and 475 subjects in third release were included in data analysis, with one scan per subject. The average age from birth at scan = 1.9 weeks; average gestational age (GA) at scan = 41.21 weeks. We only included infants who were full-term or scanned at term-equivalent age if preterm (second release: n = 399; third release: n = 607). Infants with more than 160 motion outliers were exclude (second release: n=41 dropped, third release: n = 89 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 (second release: n = 31 dropped, third release: n = 43 dropped). To identify signal dropout, we first averaged BOLD signal intensity by all the time point for each subject. From the time-averaged image, parcel-wise signals across the cortex were extracted using 100 cortical parcel scheme defined by Schaefer's atlas (Schaefer et al., 2018). The intensity of the 100 parcels gave the estimated distribution of the cortical BOLD signal. Likewise, the time-averaged BOLD intensities were extracted from the 16 ROIs used in the current study. For

each ROI, the signal dropout was identified when the BOLD intensity fell in extremely low end of the estimated BOLD signal distribution. In particular, signal intensities of 16 ROIs were transformed into z-scores using the MEAN and SD from the signal distribution of the 100 cortical parcels. Thereby the signal dropout was identified as a z-scored BOLD intensity below -3. 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 structural 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.

Neonate (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 neonates, 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 (MB) 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 (Smith et al., 2004), DPABI version 6.1 (Yan et al., 2016) 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 (Jenkinson et al., 2002), and temporally high-pass filtering (150 s). No subject had excessive head movement (> 2mm) and 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 (Behzadi et al., 2007), was used to control for these artifacts. Particularly, following the procedure described in Whitfield-Gabrieli et al. (Whitfield-Gabrieli & Nieto-Castanon, 2012) nuisance signals were extracted from 2-voxel eroded masks of spinal fluid (CSF) and white matter (WM), and the first 5 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 (Power et al., 2012, 2014). 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 neonate resting-state functional data were pre-processed by the dHCP group using the project's in-house pipeline (Fitzgibbon et al., 2020). This pipeline uses a spatial ICA-denoising step to minimize artifact due to multi-band artefact, residual head-movement, arteries, sagittal sinus, CSF pulsation. For neonates, ICA denoising is preferable to using CSF/WM regressors. 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(Fitzgibbon et al., 2020). 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 then censored from the subset, and a subject was excluded from further analyses when the number of outlier exceeded 160 (10% of the continues subset) (Hu et al., 2022).

From the preprocessed data, for both groups of adult and neonate, ROI-to-ROI connectivity was calculated using Pearson's correlation between ROI-averaged BOLD timeseries (ROI definition see below).

ROI definition

ROIs in the frontal and occipital cortices were defined from separate task-based fMRI experiments with blind and sighted adults (Kanjlia et al., 2016, 2021; Lane et al., 2015). Three experiments 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 (Lane et al., 2015). 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 (Kanjlia et al., 2016). The executive function ROIs were identified by no-go > frequent go contrast in an auditory go/no-go task with non-verbal sounds (Kanjlia et al., 2021). 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. All the ROIs were defined based on group data and were converted into each subject's native space. Any overlapping vertices between ROIs were removed and not counted toward any ROIs.

Funding

This work was supported by grants from the National Eye Institute at the National Institutes of Health (R01EY027352-01 and R01EY033340).

Acknowledgments

We would like to thank all our blind and sighted participants, the blind community and the National Federation of the Blind. Without their support, this study would not be possible. We would also like to thank the F. M. Kirby Research Center for Functional Brain Imaging at the Kennedy Krieger Institute for their assistance in data collection. Xiang Xiao was supported by the Intramural Research Program of the National Institute on Drug Abuse, the National Institute of Health, United States.

References

Abboud, S., & Cohen, L. (2019). Distinctive Interaction Between Cognitive Networks and the Visual Cortex in Early Blind Individuals. *Cerebral Cortex*, *33*(0), 4725–4742. https://doi.org/10.1093/cercor/bhz006

Amedi, A., Raz, N., Pianka, P., Malach, R., & Zohary, E. (2003). Early "visual" cortex activation correlates with superior verbal memory performance in the blind. *Nature Neuroscience*, *6*(7), 758–766. https://doi.org/10.1038/nn1072

Ashtari, M. (2020). Compensatory Cross-Modal Plasticity Persists After Sight Restoration. *Frontiers in Neuroscience*, *14*, 16.

Badde, S., Ley, P., Rajendran, S. S., Shareef, I., Kekunnaya, R., & Röder, B. (2020). Sensory experience during early sensitive periods shapes cross-modal temporal biases. *ELife*, *9*, e61238. https://doi.org/10.7554/eLife.61238

Bedny, M., Pascual-Leone, A., Dodell-Feder, D., Fedorenko, E., & Saxe, R. (2011). Language processing in the occipital cortex of congenitally blind adults. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(11), 4429–4434. https://doi.org/10.1073/pnas.1014818108

Behzadi, Y., Restom, K., Liau, J., & Liu, T. T. (2007). A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *NeuroImage*, *37*(1), 90–101. https://doi.org/10.1016/j.neuroimage.2007.04.042

Biswal, B., Zerrin Yetkin, F., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar mri. *Magnetic Resonance in Medicine*, *34*(4), 537–541. https://doi.org/10.1002/mrm.1910340409

Burton, H., Sinclair, R. J., & Agato, A. (2012). Recognition memory for Braille or spoken words: An fMRI study in early blind. *Brain Research*, *1438*, 22–34. https://doi.org/10.1016/j.brainres.2011.12.032

Burton, H., Snyder, A. Z., & Raichle, M. E. (2014). Resting state functional connectivity in early blind humans. *Frontiers in Systems Neuroscience*, *8*(1 APR), 1–13. https://doi.org/10.3389/fnsys.2014.00051

Collignon, O., Vandewalle, G., Voss, P., Albouy, G., Charbonneau, G., Lassonde, M., & Lepore, F. (2011). Functional specialization for auditory-spatial processing in the occipital cortex of congenitally blind humans. *Proceedings of the National Academy of Sciences*, *108*(11), 4435–4440. https://doi.org/10.1073/pnas.1013928108

Crair, M. C., Gillespie, D. C., & Stryker, M. P. (1998). The Role of Visual Experience in the Development of Columns in Cat Visual Cortex. *Science*, *279*(5350), 566–570. https://doi.org/10.1126/science.279.5350.566

Diedenhofen, B., & Musch, J. (2015). cocor: A Comprehensive Solution for the Statistical Comparison of Correlations. *PLOS ONE*, *10*(4), e0121945. https://doi.org/10.1371/journal.pone.0121945

Doria, V., Beckmann, C. F., Arichi, T., Merchant, N., Groppo, M., Turkheimer, F. E., Counsell, S. J., Murgasova, M., Aljabar, P., Nunes, R. G., Larkman, D. J., Rees, G., & Edwards, A. D. (2010). Emergence of resting state networks in the preterm human brain. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(46), 20015–20020. https://doi.org/10.1073/pnas.1007921107

Espinosa, J. S., & Stryker, M. P. (2012). Development and Plasticity of the Primary Visual Cortex. *Neuron*, *75*(2), 230–249. https://doi.org/10.1016/j.neuron.2012.06.009

Fitzgibbon, S. P., Harrison, S. J., Jenkinson, M., Baxter, L., Robinson, E. C., Bastiani, M., Bozek, J., Karolis, V., Cordero Grande, L., Price, A. N., Hughes, E., Makropoulos, A., Passerat-Palmbach, J., Schuh, A., Gao, J., Farahibozorg, S. R., O'Muircheartaigh, J., Ciarrusta, J., O'Keeffe, C., … Andersson, J. (2020). The developing Human

Connectome Project (dHCP) automated resting-state functional processing framework for newborn infants. *NeuroImage*, *223*(August), 117303. https://doi.org/10.1016/j.neuroimage.2020.117303

Fransson, P., Skiöld, B., Engström, M., Hallberg, B., Mosskin, M., Åden, U., Lagercrantz, H., & Blennow, M. (2009). Spontaneous brain activity in the newborn brain during natural sleep-an fMRI study in infants born at full term. *Pediatric Research*, *66*(3), 301–305. https://doi.org/10.1203/PDR.0b013e3181b1bd84

Gao, W., Zhu, H., Giovanello, K. S., Smith, J. K., Shen, D., Gilmore, J. H., & Lin, W. (2009). Evidence on the emergence of the brain's default network from 2-week-old to 2-year-old healthy pediatric subjects. *Proceedings of the National Academy of Sciences*, *106*(16), 6790–6795. https://doi.org/10.1073/pnas.0811221106

Guerreiro, M. J. S., Putzar, L., & Röder, B. (2015). The effect of early visual deprivation on the neural bases of multisensory processing. *Brain*, *138*(6), 1499–1504. https://doi.org/10.1093/brain/awv076

Hensch, T. K. (2005). Critical period plasticity in local cortical circuits. *Nature Reviews Neuroscience*, *6*(11), 877–888. https://doi.org/10.1038/nrn1787

Horton, J. C., & Hocking, D. R. (1996). An adult-like pattern of ocular dominance columns in striate cortex of newborn monkeys prior to visual experience. *Journal of Neuroscience*, *16*(5), 1791–1807. https://doi.org/10.1523/JNEUROSCI.16-05-01791.1996

Hu, H., Cusack, R., & Naci, L. (2022). Typical and disrupted brain circuitry for conscious awareness in full-term and preterm infants. *Brain Communications*, *4*(2), fcac071. https://doi.org/10.1093/braincomms/fcac071

Hubel, D. H., & Wiesel, T. N. (1970). The period of susceptibility to the physiological effects of unilateral eye closure in kittens. *The Journal of Physiology*, *206*(2), 419–436. https://doi.org/10.1113/jphysiol.1970.sp009022

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *NeuroImage*, *17*(2), 825–841. https://doi.org/10.1016/s1053-8119(02)91132-8

Kanjlia, S., Lane, C., Feigenson, L., & Bedny, M. (2016). Absence of visual experience modifies the neural basis of numerical thinking. *Proceedings of the National Academy of Sciences of the United States of America*, *113*(40), 11172–11177. https://doi.org/10.1073/pnas.1524982113

Kanjlia, S., Loiotile, R. E., Harhen, N., & Bedny, M. (2021). 'Visual' cortices of congenitally blind adults are sensitive to response selection demands in a go/no-go task. *NeuroImage*, *236*(April), 118023. https://doi.org/10.1016/j.neuroimage.2021.118023

Katz, L. C., & Crowley, J. C. (2002). Development of cortical circuits: Lessons from ocular dominance columns. *Nature Reviews Neuroscience*, *3*(1), Article 1. https://doi.org/10.1038/nrn703

Klinge, C., Eippert, F., Röder, B., & Büchel, C. (2010). Corticocortical connections mediate primary visual cortex responses to auditory stimulation in the blind. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *30*(38), 12798–12805. https://doi.org/10.1523/JNEUROSCI.2384-10.2010

Lane, C., Kanjlia, S., Omaki, A., & Bedny, M. (2015). "Visual" cortex of congenitally blind adults responds to syntactic movement. *Journal of Neuroscience*, *35*(37), 12859–12868. https://doi.org/10.1523/JNEUROSCI.1256-15.2015

Lane, C., Kanjlia, S., Richardson, H., Fulton, A., Omaki, A., & Bedny, M. (2017). Reduced Left Lateralization of Language in Congenitally Blind Individuals. *Journal of Cognitive Neuroscience*, *29*(1), 65–78. https://doi.org/10.1162/jocn_a_01045

Le Grand, R., Mondloch, C. J., Maurer, D., & Brent, H. P. (2001). Early visual experience and face processing. *Nature*, *410*(6831), 890–890. https://doi.org/10.1038/35073749

Lewis, C. M., Baldassarre, A., Committeri, G., Romani, G. L., & Corbetta, M. (2009). Learning sculpts the spontaneous activity of the resting human brain. *Proceedings of the National Academy of Sciences*, *106*(41), 17558–17563. https://doi.org/10.1073/pnas.0902455106

Li, Y., Fitzpatrick, D., & White, L. E. (2006). The development of direction selectivity in ferret visual cortex requires early visual experience. *Nature Neuroscience*, *9*(5), 676–681. https://doi.org/10.1038/nn1684

Liu, W. C., Flax, J. F., Guise, K. G., Sukul, V., & Benasich, A. A. (2008). Functional connectivity of the sensorimotor area in naturally sleeping infants. *Brain Research*, *1223*, 42–49. https://doi.org/10.1016/j.brainres.2008.05.054

Liu, Y., Yu, C., Liang, M., Li, J., Tian, L., Zhou, Y., Qin, W., Li, K., & Jiang, T. (2007). Whole brain functional connectivity in the early blind. *Brain*, *130*(8), 2085–2096. https://doi.org/10.1093/brain/awm121

Masuda, Y., Takemura, H., Terao, M., Miyazaki, A., Ogawa, S., Horiguchi, H., Nakadomari, S., Matsumoto, K., Nakano, T., Wandell, B. A., & Amano, K. (2021). V1 Projection Zone Signals in Human Macular Degeneration Depend on Task Despite Absence of Visual Stimulus. *Current Biology*, *31*(2), 406-412.e3. https://doi.org/10.1016/j.cub.2020.10.034

Maurer, D., Mondloch, C. J., & Lewis, T. L. (2007). Effects of early visual deprivation on perceptual and cognitive development. In *Progress in Brain Research* (Vol. 164, pp. 87–104). Elsevier. https://doi.org/10.1016/S0079-6123(07)64005-9

McKyton, A., Ben-Zion, I., Doron, R., & Zohary, E. (2015). The Limits of Shape Recognition following Late Emergence from Blindness. *Current Biology*, *25*(18), 2373–2378. https://doi.org/10.1016/j.cub.2015.06.040

Molnár, Z., Luhmann, H. J., & Kanold, P. O. (2020). Transient cortical circuits match spontaneous and sensory-driven activity during development. *Science*, *370*(6514), eabb2153. https://doi.org/10.1126/science.abb2153

Pearson, K., & Filon, L. N. G. (1898). Mathematical contributions to the theory of evolution. IV. On the probable errors of frequency constants and on the influence of random selection on variation and correlation. *Proceedings of the Royal Society of London*, *62*(379–387), 173–176. https://doi.org/10.1098/rspl.1897.0091

Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *NeuroImage*, *59*(3), 2142–2154. https://doi.org/10.1016/j.neuroimage.2011.10.018

Power, J. D., Mitra, A., Laumann, T. O., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2014). Methods to detect, characterize, and remove motion artifact in resting state fMRI. *NeuroImage*, *84*, 320–341. https://doi.org/10.1016/j.neuroimage.2013.08.048

Reh, R. K., Dias, B. G., Nelson, C. A., Kaufer, D., Werker, J. F., Kolb, B., Levine, J. D., & Hensch, T. K. (2020). Critical period regulation across multiple timescales. *Proceedings of the National Academy of Sciences*, *117*(38), 23242–23251. https://doi.org/10.1073/pnas.1820836117

Rochefort, N. L., Narushima, M., Grienberger, C., Marandi, N., Hill, D. N., & Konnerth, A. (2011). Development of Direction Selectivity in Mouse Cortical Neurons. *Neuron*, *71*(3), 425–432. https://doi.org/10.1016/j.neuron.2011.06.013

Röder, B., & Kekunnaya, R. (2021). Visual experience dependent plasticity in humans. *Current Opinion in Neurobiology*, *67*, 155–162. https://doi.org/10.1016/j.conb.2020.11.011

Sadato, N., Pascual-Leone, A., Grafman, J., Ibañez, V., Deiber, M., Dold, G., & Hallett, M. (1996). Activation of the primary visual cortex by Braille reading in blind subjects. *Nature*, *380*(6574), 526–528. https://doi.org/10.1038/380526a0

Schaefer, A., Kong, R., Gordon, E. M., Laumann, T. O., Zuo, X.-N., Holmes, A. J., Eickhoff, S. B., & Yeo, B. T. T. (2018). Local-Global Parcellation of the Human Cerebral Cortex from Intrinsic Functional Connectivity MRI. *Cerebral Cortex*, *28*(9), 3095–3114. https://doi.org/10.1093/cercor/bhx179

Sengpiel, F., & Kind, P. C. (2002). The Role of Activity in Development of the Visual System. *Current Biology*, *12*(23), R818–R826. https://doi.org/10.1016/S0960-9822(02)01318-0

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., Bannister, P. R., De Luca, M., Drobnjak, I., Flitney, D. E., Niazy, R. K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J. M., & Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, *23*(SUPPL. 1), 208–219. https://doi.org/10.1016/j.neuroimage.2004.07.051

Stevens, W. D., Buckner, R. L., & Schacter, D. L. (2010). Correlated Low-Frequency BOLD Fluctuations in the Resting Human Brain Are Modulated by Recent Experience in Category-Preferential Visual Regions. *Cerebral Cortex*, *20*(8), 1997–2006. https://doi.org/10.1093/cercor/bhp270

Striem-Amit, E., Ovadia-Caro, S., Caramazza, A., Margulies, D. S., Villringer, A., & Amedi, A. (2015). Functional connectivity of visual cortex in the blind follows retinotopic organization principles. *Brain*, *138*(6), 1679–1695. https://doi.org/10.1093/brain/awv083

Tian, M., Saccone, E. J., Kim, J. S., Kanjlia, S., & Bedny, M. (2022). Sensory modality and spoken language shape reading network in blind readers of Braille. *Cerebral Cortex*.

Watkins, K. E., Cowey, A., Alexander, I., Filippini, N., Kennedy, J. M., Smith, S. M., Ragge, N., & Bridge, H. (2012). Language networks in anophthalmia: Maintained hierarchy of processing in "visual" cortex. *Brain*, *135*(5), 1566–1577. https://doi.org/10.1093/brain/aws067

Whitfield-Gabrieli, S., & Nieto-Castanon, A. (2012). Conn: A Functional Connectivity Toolbox for Correlated and Anticorrelated Brain Networks. *Brain Connectivity*, *2*(3), 125–141. https://doi.org/10.1089/brain.2012.0073

Yan, C.-G., Wang, X.-D., Zuo, X.-N., & Zang, Y.-F. (2016). DPABI: Data Processing & Analysis for (Resting-State) Brain Imaging. *Neuroinformatics*, *14*(3), 339–351. https://doi.org/10.1007/s12021-016-9299-4

Yu, C., Liu, Y., Li, J., Zhou, Y., Wang, K., Tian, L., Qin, W., Jiang, T., & Li, K. (2008). Altered functional connectivity of primary visual cortex in early blindness. *Human Brain Mapping*, *29*(5), 533–543. https://doi.org/10.1002/hbm.20420

Zhang, H., Shen, D., & Lin, W. (2019). Resting-state functional MRI studies on infant brains: A decade of gap-filling efforts. *NeuroImage*, *185*(July 2018), 664–684. https://doi.org/10.1016/j.neuroimage.2018.07.004