

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 like those of sighted adults and blindness causes reorganization? Alternatively, do infants start like 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, $n = 475$). 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. Specifically, 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 (PFC). In blind adults, visual cortices show stronger coupling with PFC. In infants, connectivity of secondary visual cortices is stronger with PFC, while V1 shows equal sensory-motor/PFC connectivity. In contrast, lateralization of occipital-to-frontal connectivity resembles the sighted adults at birth and is reorganized by blindness, possibly due to recruitment of occipital networks for lateralized cognitive functions, such as language.

eLife assessment

This **important** study provides evidence supporting the idea that visual experience plays a role in shaping the patterns of functional connectivity between extrastriate visual cortex and prefrontal regions during development, by comparing neonates, blind and sighted adults. The evidence supporting the authors' claim is **solid**, although control analyses could strengthen the conclusions and possibly offer additional mechanistic insights. This study will be of significant interest to neuroscientists and neuroimaging researchers working on vision, plasticity, and development.

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 (Bedny et al., 2011 [↗](#); Burton et al., 2012 [↗](#); Collignon et al., 2011 [↗](#); Kanjlia et al., 2016 [↗](#), 2021 [↗](#); Lane et al., 2015 [↗](#); Masuda et al., 2021 [↗](#); N. Raz et al., 2005 [↗](#); Sadato et al., 1996 [↗](#)). Occipital cortices of blind adults also show distinctive patterns of spontaneous neural activity and functional connectivity (resting state correlations) with non-visual networks (Abboud & Cohen, 2019 [↗](#); Bedny et al., 2011 [↗](#); Burton et al., 2014 [↗](#); Butt et al., 2013 [↗](#); Deen et al., 2015 [↗](#); Y. Liu et al., 2007 [↗](#); Striem-Amit et al., 2015 [↗](#); Watkins et al., 2012 [↗](#)). 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 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, n = 475). We used resting state data as a common measure of cortical function across these diverse populations.

Previous resting state studies comparing sighted infants to sighted adults have largely reported similarities, implying a ‘prepared’ sighted pattern (Barttfeld et al., 2018 [↗](#); 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 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 differs across blind and sighted adults.

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 (Kanjlia et al., 2016 [↗](#), 2021 [↗](#); Lane et al., 2015 [↗](#)). In blind adults, these three regions respond to different higher-cognitive tasks, including language, numerical reasoning and executive control (Kanjlia et al., 2016 [↗](#), 2021 [↗](#); Lane et al., 2015 [↗](#)). In sighted people, these regions roughly correspond to the

anatomical location of areas such as motion area V5/MT+, the lateral occipital complex (LO), V3a and V4v (Tootell et al., 1997 [↗](#); Van Essen et al., 2001 [↗](#)). Although their precise visual function in sighted people is not known. 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 (Amedi et al., 2003 [↗](#); Bedny et al., 2011 [↗](#); Burton et al., 2014 [↗](#); Butt et al., 2013 [↗](#); Lane et al., 2015 [↗](#); N. Raz et al., 2005 [↗](#); Sadato et al., 1996 [↗](#); Striem-Amit et al., 2015 [↗](#); Yu et al., 2008 [↗](#)). 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.

Results

Connectivity profile of secondary visual cortices in sighted infants is 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 Figure S1 for the connectivity matrices).

These results suggests that vision is required to set up the sighted adult functional connectivity pattern, i.e., vision enhances occipital 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, 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 Figure S2). Next, 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 Figure S3 to Supplementary Figure S6). We performed this validation procedure for all analyses reported below with similar results.

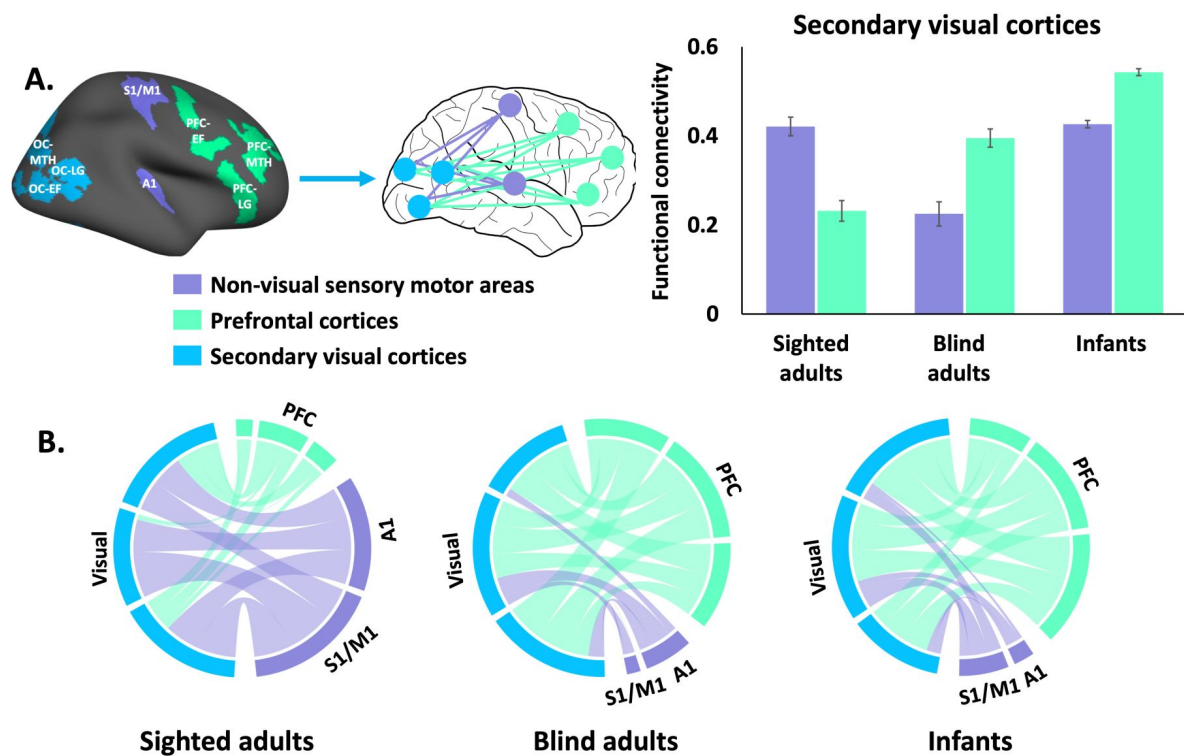


Figure 1

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. Note that regions extend to ventral surface, not shown. See Supplementary Figure S7 for the full views of ROIs. (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

As for secondary visual cortices, 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** [↗](#)).

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 Figure S1 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 Figure S8). A few weeks of vision after birth is therefore insufficient to influence connectivity.

Evidence for blindness-related reorganization in laterality of occipito-frontal connectivity

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: $t_{(29)} = 7.019$, $p < 0.001$).

These connectivity results are consistent with previous studies of task-based cross-modal responses in blindness. In blind adults cross-modal responses in occipital cortex and co-lateralize with fronto-parietal networks with related functions (Kanjlila et al., 2021 [↗](#); Lane et al., 2017 [↗](#)). For example, language-responsive occipital areas collateralize with language responsive prefrontal areas across individuals (Lane et al., 2017 [↗](#)).

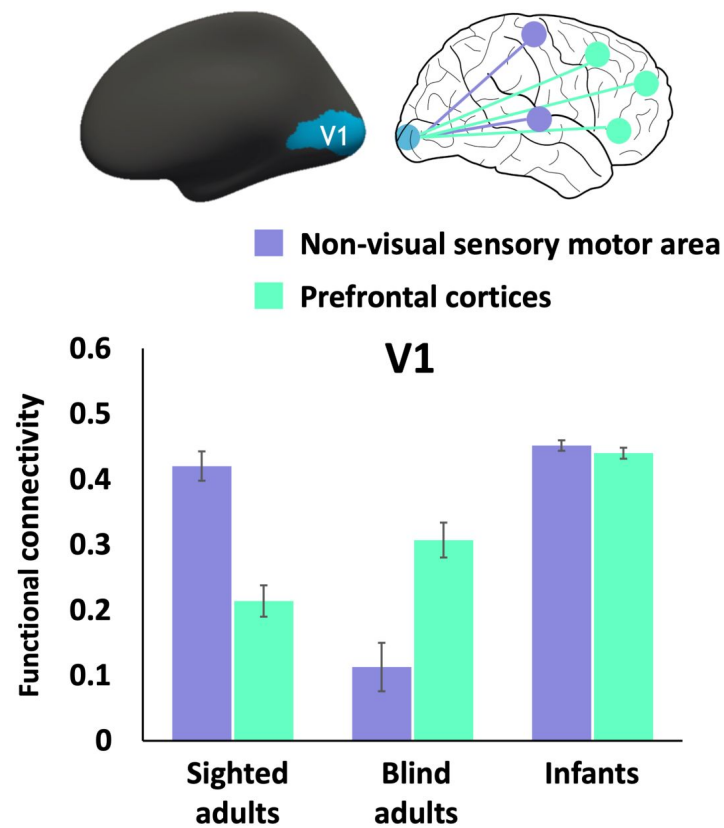


Figure 2

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).

The connectivity pattern of sighted infants resembled sighted more than blind adults (**Fig. 3**), suggesting 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: $F_{(1, 503)} = 303.04$, $p < 0.001$). By contrast, 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, which is observed in task-based studies, may drive stronger within-hemisphere connectivity in this population (Kanjlia et al., 2021; Lane et al., 2017; Tian et al., 2022).

Specialization across different fronto-occipital networks: present in adults, absent at birth

It is not the case that every occipital area shows equal connectivity to every prefrontal area. On the contrary, in blind adults resting state connectivity patterns are specialized and aligned with the functional specialization observed in task-based data (Bedny et al., 2011; 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 (**Fig. 4**) (Bedny et al., 2011; Kanjlia et al., 2016, 2021; Lane et al., 2015). 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 (Kanjlia et al., 2016, 2021; Lane et al., 2015). 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 Figure S9 for all three regions).

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 Figure S9). 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 were 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 showed stronger connectivity to math and response-conflict areas of PFC in infants, this biased against language areas was smaller for this occipital areas than the other two.

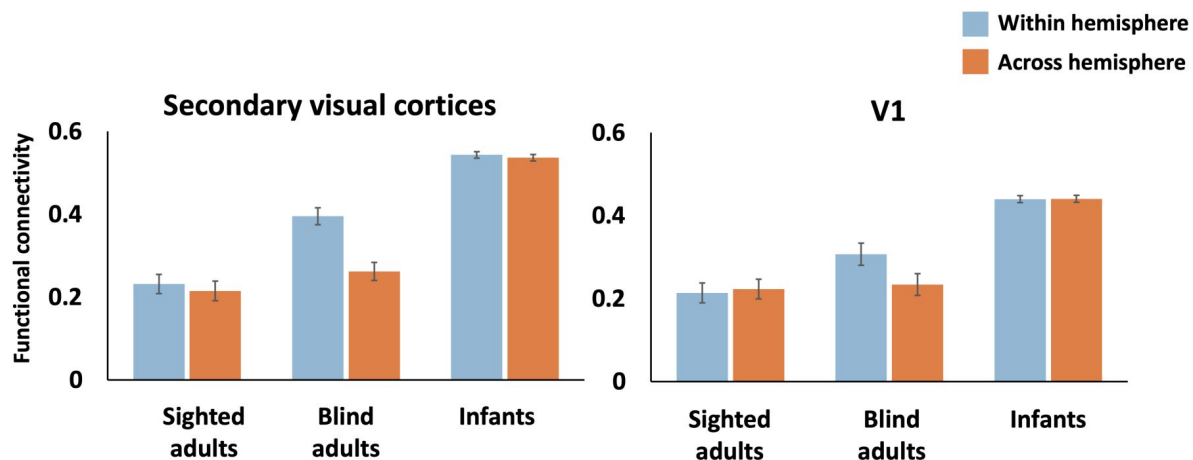


Figure 3

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.

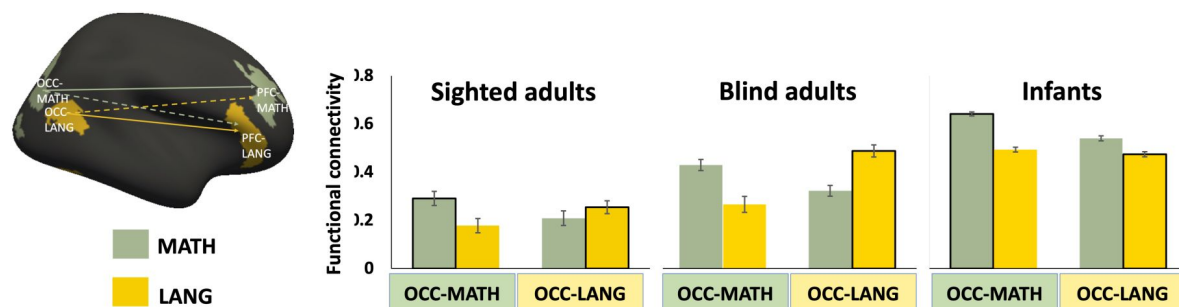


Figure 4

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 (Kanjlila et al., 2016 [DOI](#), 2021 [DOI](#); Lane et al., 2015 [DOI](#)). PFC/OCC-MATH: math-responsive regions were more active when solving math equations than comprehending sentences. PFC/OCC-LANG: language-responsive regions were more active when comprehending sentences than solving math equations (Kanjlila et al., 2016 [DOI](#), 2021 [DOI](#); Lane et al., 2015 [DOI](#)). 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. See Supplementary Figure S10 for connectivity matrix.

Note that findings regarding regional specialization need to be interpreted with caution for two reasons. First, although, prior evidence suggests that at least some of the prefrontal specialization present in adults is already present even in young babies, we do not know whether the language/number/executive function distinctions exist in prefrontal cortices of infants (Raz & Saxe, 2020 [DOI](#)). Second, these more fine-grained comparisons across occipital/frontal regions are more vulnerable to potential anatomical alignment issues between adult and infant brains. In other words, lack of specialization in infants could reflect the different location of the areas in this population.

Discussion

The sighted adult functional connectivity pattern, although the most common in the population, is not the 'default' starting state in infants 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, although there was no comparison to blind adults in that study (Barttfeld et al., 2018 [DOI](#)). In V1, infants fell somewhere in between sighted and blind adults, suggesting an effect both of vision and of blindness on functional connectivity. We hypothesize that vision, as well as temporally coordinated multi-modal experiences contribute to establishing the sighted connectivity profile.

Since visual behavior is likely to be influenced by the communication of visual cortices with non-visual networks, a key question concerns the behavioral relevance of these connectivity signatures for vision and multimodal integration. 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 (Ashtari, 2020 [DOI](#); Badde et al., 2020 [DOI](#); Guerreiro et al., 2015 [DOI](#); Putzar et al., 2007 [DOI](#)). There is also evidence that occipital oscillations, which affect cross-network communication, are different in this population (Pant et al., 2023 [DOI](#)). 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. Habitual activation of occipital networks during higher cognitive tasks in early development could then itself influence both connectivity and selectivity, resulting in different adult profiles.

The clearest evidence for blindness-related reorganization in the current study was observed in the case of laterality. Connectivity lateralization in sighted infants resembles that of sighted adults, in both V1 and secondary visual cortices. Said differently, relative to both sighted infants and sighted adults, blind adults 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 (Lane et al., 2017 [DOI](#)). We speculate that habitual activation of visual cortices by higher-cognitive tasks, such as language, which are themselves highly lateralized, contributes to this biased connectivity pattern of occipital cortex in blindness.

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, $t_{(78)} = 0.05$, $p = 0.996$). Since blind participants were on average older, we also performed analyses in an age-matched subgroups of sighted controls ($n = 29$) and found similar results to the full sample (see Supplementary Figure S11 to Figure S14). 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.developingconnectome.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 excluded ($n = 116$ 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 parcels defined by Schaefer's atlas (Schaefer et al., 2018). 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 = $2.4 \times 2.4 \times 2.5$ mm, inter-slice gap = 0.5 mm, field of view (FOV) = $192 \times 172.8 \times 107.5$. 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 $0.8 \times 0.8 \text{ mm}^2$ and 1.6 mm slices overlapped by 0.8 mm (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 = 38 ms, 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 [DOI](#)), DPABI version 6.1 (Yan et al., 2016 [DOI](#)), FreeSurfer (Dale et al., 1999 [DOI](#)), 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 [DOI](#)), and temporally high-pass filtering (150 s). No subject had excessive head movement ($> 2\text{mm}$) or rotation ($> 2^\circ$) 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 [DOI](#)), was therefore used to control for these artifacts. Particularly, following the procedure described in Whitfield-Gabrieli *et al.*, 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 (Whitfield-Gabrieli & Nieto-Castanon, 2012 [DOI](#)). In addition, a scrubbing procedure was applied to further reduce the effect of motion on functional connectivity measures (Power et al., 2012 [DOI](#), 2014 [DOI](#)). 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 (Fitzgibbon et al., 2020 [DOI](#)). 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 (Fitzgibbon et al., 2020 [DOI](#)). 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) (Hu et al., 2022 [DOI](#)).

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 (Diedenhofen & Musch, 2015 [↗](#); Pearson & Filon, 1898 [↗](#)).

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 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.

The V1 was defined from a previously published anatomical surface-based atlas (PALS-B12) (Van Essen, 2005 [↗](#)). 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”) (Kanjlia et al., 2021 [↗](#)). The primary auditory cortex (A1) ROI was defined as the transverse temporal portion of a gyral-based atlas (Desikan et al., 2006 [↗](#); Morosan et al., 2001 [↗](#)).

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 (Bozek et al., 2018 [↗](#)). ANTS, previously shown to be effective in pediatric studies (Avants et al., 2014 [↗](#); Cabral et al., 2022 [↗](#); Jain et al., 2012 [↗](#); Lawson et al., 2013 [↗](#)), 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* (Cabral et al., 2022 [↗](#)). 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 Figure S15). 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.developingconnectome.org> [↗](#)). The de-identified blind and sighted adults' data will be posted on *Vivli.org* [↗](#) upon publication of the current manuscript.

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Competing interests

The authors report no competing interests.

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Reviewer #1 (Public Review):

Summary:

The present study evaluates the role of visual experience in shaping functional correlations between extrastriate visual cortex and frontal regions. The authors used fMRI to assess "resting-state" temporal correlations in three groups: sighted adults, congenitally blind adults, and neonates. Previous research has already demonstrated differences in functional correlations between visual and frontal regions in sighted compared to early blind individuals. The novel contribution of the current study lies in the inclusion of an infant dataset, which allows for an assessment of the developmental origins of these differences.

The main results of the study reveal that correlations between prefrontal and visual regions are more prominent in the blind and infant groups, with the blind group exhibiting greater lateralization. Conversely, correlations between visual and somato-motor cortices are more prominent in sighted adults. Based on these data, the authors conclude that visual experience plays an instructive role in shaping these cortical networks. This study provides valuable insights into the impact of visual experience on the development of functional connectivity in the brain.

Strengths:

The dissociations in functional correlations observed among the sighted adult, congenitally blind, and neonate groups provide strong support for the study's main conclusion regarding experience-driven changes in functional connectivity profiles between visual and frontal regions.

In general, the findings in sighted adult and congenitally blind groups replicate previous studies and enhance the confidence in the reliability and robustness of the current results.

Split-half analysis provides a good measure of robustness in the infant data.

Weaknesses:

There is some ambiguity in determining which aspects of these networks are shaped by experience.

This uncertainty is compounded by notable differences in data acquisition and preprocessing methods, which could result in varying signal quality across groups. Variations in signal quality may, in turn, have an impact on the observed correlation patterns.

The study's findings could benefit from being situated within a broader debate surrounding the instructive versus permissive roles of experience in the development of visual circuits.

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Reviewer #2 (Public Review):

Summary:

Tian et al. explore the developmental origins of cortical reorganization in blindness. Previous work has found that a set of regions in the occipital cortex show different functional responses and patterns of functional correlations in blind vs. sighted adults. In this paper, Tian et al. ask: how does this organization arise over development? Is the "starting state" more like the blind pattern, or more like the adult pattern? Their analyses reveal that the answer depends on the particular networks investigated; some functional connections in

infants look more like blind than sighted adults; other functional connections look more like sighted than blind adults; and others fall somewhere in the middle, or show an altogether different pattern in infants compared with both sighted and blind adults.

Strengths:

The question raised in this paper is extremely important: what is the starting state in development for visual cortical regions, and how is this organization shaped by experience? This paper is among the first to examine this question, particularly by comparing infants not only with sighted adults but also blind adults, which sheds new light on the role of visual (and cross-modal) experience. Another clear strength lies in the unequivocal nature of many results. Many results have very large effect sizes, critical interactions between regions and groups are tested and found, and infant analyses are replicated in split halves of the data.

Weaknesses:

A central claim is that "infant secondary visual cortices functionally resemble those of blind more than sighted adults" (abstract, last paragraph of intro). I see two potential issues with this claim. First, a minor change: given the approaches used here, no claims should be made about the "function" of these regions, but rather their "functional correlations". Second (and more importantly), the claim that the secondary visual cortex in general resembles blind more than sighted adults is still not fully supported by the data. In fact, this claim is only true for one aspect of secondary visual area functional correlations (i.e., their connectivity to A1/M1/S1 vs. PFC). In other analyses, the infant secondary visual cortex looks more like sighted adults than blind adults (i.e., in within vs. across hemisphere correlations), or shows a different pattern from both sighted and blind adults (i.e., in occipito-frontal subregion functional connectivity). It is not clear from the manuscript why the comparison to PFC vs. non-visual sensory cortex is more theoretically important than hemispheric changes or within-PFC correlations (in fact, if anything, the within-PFC correlations strike me as the most important for understanding the development and reorganization of these secondary visual regions). It seems then that a more accurate conclusion is that the secondary visual cortex shows a mix of instructive effects of vision and reorganizing effects of blindness, albeit to a different extent than the primary visual cortex.

Relatedly, group differences in overall secondary visual cortex connectivity are particularly striking as visualized in the connectivity matrices shown in Figure S1. In the results (lines 105-112), it is noted that while the infant FC matrix is strongly correlated with both adult groups, the infant group is nonetheless more strongly correlated with the blind than sighted adults. I am concerned that these results might be at least partially explained by distance (i.e., local spread of the bold signal), since a huge portion of the variance in these FC matrices is driven by stronger correlations between regions within the same system (e.g., secondary-secondary visual cortex, frontal-frontal cortex), which are inherently closer together, relative to those between different systems (e.g., visual to frontal cortex). How do results change if only comparisons between secondary visual regions and non-visual regions are included (i.e., just the pairs of regions within the bold black rectangle on the figure), which limits the analysis to long-rang connections only? Indeed, looking at the off-diagonal comparisons, it seems that in fact there are three altogether different patterns here in the three groups. Even if the correlation between the infant pattern and blind adult pattern survives, it might be more accurate to claim that infants are different from both adult groups, suggesting both instructive effects of vision and reorganizing effects of blindness. It might help to show the correlation between each group and itself (across independent sets of subjects) to better contextualize the relative strength of correlations between the groups.

It is not clear that differences between groups should be attributed to visual experience only. For example, despite the title of the paper, the authors note elsewhere that cross-modal experience might also drive changes between groups. Another factor, which I do not see discussed, is possible ongoing experience-independent maturation. The infants scanned are

extremely young, only 2 weeks old. Although no effects of age are detected, it is possible that cortex is still undergoing experience-independent maturation at this very early stage of development. For example, consider Figure 2; perhaps V1 connectivity is not established at 2 weeks, but eventually achieves the adult pattern later in infancy or childhood. Further, consider the possibility that this same developmental progression would be found in infants and children born blind. In that case, the blind adult pattern may depend on blindness-related experience only (which may or may not reflect "visual" experience per se). To deal with these issues, the authors should add a discussion of the role of maturation vs. experience and temper claims about the role of visual experience specifically (particularly in the title).

The authors measure functional correlations in three very different groups of participants and find three different patterns of functional correlations. Although these three groups differ in critical, theoretically interesting ways (i.e., in age and visual/cross-modal experience), they also differ in many uninteresting ways, including at least the following: sampling rate (TR), scan duration, multi-band acceleration, denoising procedures (CompCor vs. ICA), head motion, ROI registration accuracy, and wakefulness (I assume the infants are asleep).

Addressing all of these issues is beyond the scope of this paper, but I do feel the authors should acknowledge these confounds and discuss the extent to which they are likely (or not) to explain their results. The authors would strengthen their conclusions with analyses directly comparing data quality between groups (e.g., measures of head motion and split-half reliability would be particularly effective).

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Reviewer #3 (Public Review):

Summary:

This study aimed to investigate whether the differences observed in the organization of visual brain networks between blind and sighted adults result from a reorganization of an early functional architecture due to blindness, or whether the early architecture is immature at birth and requires visual experience to develop functional connections. This question was investigated through the comparison of 3 groups of subjects with resting-state functional MRI (rs-fMRI). Based on convincing analyses, the study suggests that: 1) secondary visual cortices showed higher connectivity to prefrontal cortical regions (PFC) than to non-visual sensory areas (S1/M1 and A1) in sighted infants like in blind adults, in contrast to sighted adults; 2) the V1 connectivity pattern of sighted infants lies between that of sighted adults (stronger functional connectivity with non-visual sensory areas than with PFC) and that of blind adults (stronger functional connectivity with PFC than with non-visual sensory areas); 3) the laterality of the connectivity patterns of sighted infants resembled those of sighted adults more than those of blind adults, but sighted infants showed a less differentiated fronto-occipital connectivity pattern than adults.

Strengths:

- The question investigated in this article is important for understanding the mechanisms of plasticity during typical and impaired development, and the approach considered, which compares different groups of subjects including, neonates/infants and blind adults, is highly original.
- Overall, the analyses considered are solid and well-detailed. The results are quite convincing, even if the interpretation might need to be revised downwards, as factors other than visual experience may play a role in the development of functional connections with the visual system.

Weaknesses:

- While it is informative to compare the "initial" state (close to birth) and the "final" states in blind and sighted adults to study the impact of post-natal and visual experience, this study does not analyze the chronology of this development and when the specialization of functional connections is completed. This would require investigating when experience-dependent mechanisms are important for the setting- establishment of multiple functional connections within the visual system. This could be achieved by analyzing different developmental periods in the same way, using open databases such as the Baby Connectome Project. Given the early, "condensed" maturation of the visual system after birth, we might expect sighted infants to show connectivity patterns similar to those of adults a few months after birth.
 - The rationale for mixing full-term neonates and preterm infants (scanned at term-equivalent age) from the dHCP 3rd release is not understandable since preterms might have a very different development related to prematurity and to post-natal (including visual) experience. Although the authors show that the difference between the connectivity of visual and other sensory regions, and the one of visual and PFC regions, do not depend on age at birth, they do not show that each connectivity pattern is not influenced by prematurity. Simply not considering the preterm infants would have made the analysis much more robust, and the full-term group in itself is already quite large compared with the two adult groups. The current study setting and the analyses performed do not seem to be an adequate and sufficient model to ascertain that "a few weeks of vision after birth is ... insufficient to influence connectivity".
- In a similar way, excluding the few infants with detected brain anomalies (radiological scores higher or equal to 4) would strengthen the group homogeneity by focusing on infants supposed to have a rather typical neurodevelopment. The authors quote all infants as "sighted" but this is not guaranteed as no follow-up is provided.
- The post-menstrual age (PMA) at scan of the infants is also not described. The methods indicate that all were scanned at "term-equivalent age" but does this mean that there is some PMA variability between 37 and 41 weeks? Connectivity measures might be influenced by such inter-individual variability in PMA, and this could be evaluated.
- The rationale for presenting results on the connectivity of secondary visual cortices before one of the primary cortices (V1) was not clear to understand. Also, it might be relevant to better justify why only the connectivity of visual regions to non-visual sensory regions (S1-M1, A1) and prefrontal cortex (PFC) was considered in the analyses, and not the ones to other brain regions.
 - In relation to the question explored, it might be informative to reposition the study in relation to what others have shown about the developmental chronology of structural and functional long-distance and short-distance connections during pregnancy and the first postnatal months.
 - The authors acknowledge the methodological difficulties in defining regions of interest (ROIs) in infants in a similar way as adults. The reliability and the comparability of the ROIs positioning in infants is definitely an issue. Given that brain development is not homogeneous and synchronous across brain regions (in particular with the frontal and parietal lobes showing delayed growth), the newborn brain is not homothetic to the adult brain, which poses major problems for registration. The functional specialization of cortical regions is incomplete at birth. This raises the question of whether the findings of this study would be stable/robust if slightly larger or displaced regions had been considered, to cover with greater certainty the same areas as those considered in adults. And have other cortical

parcellation approaches been considered to assess the ROIs robustness (e.g. MCRIB-S for full-terms)?

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