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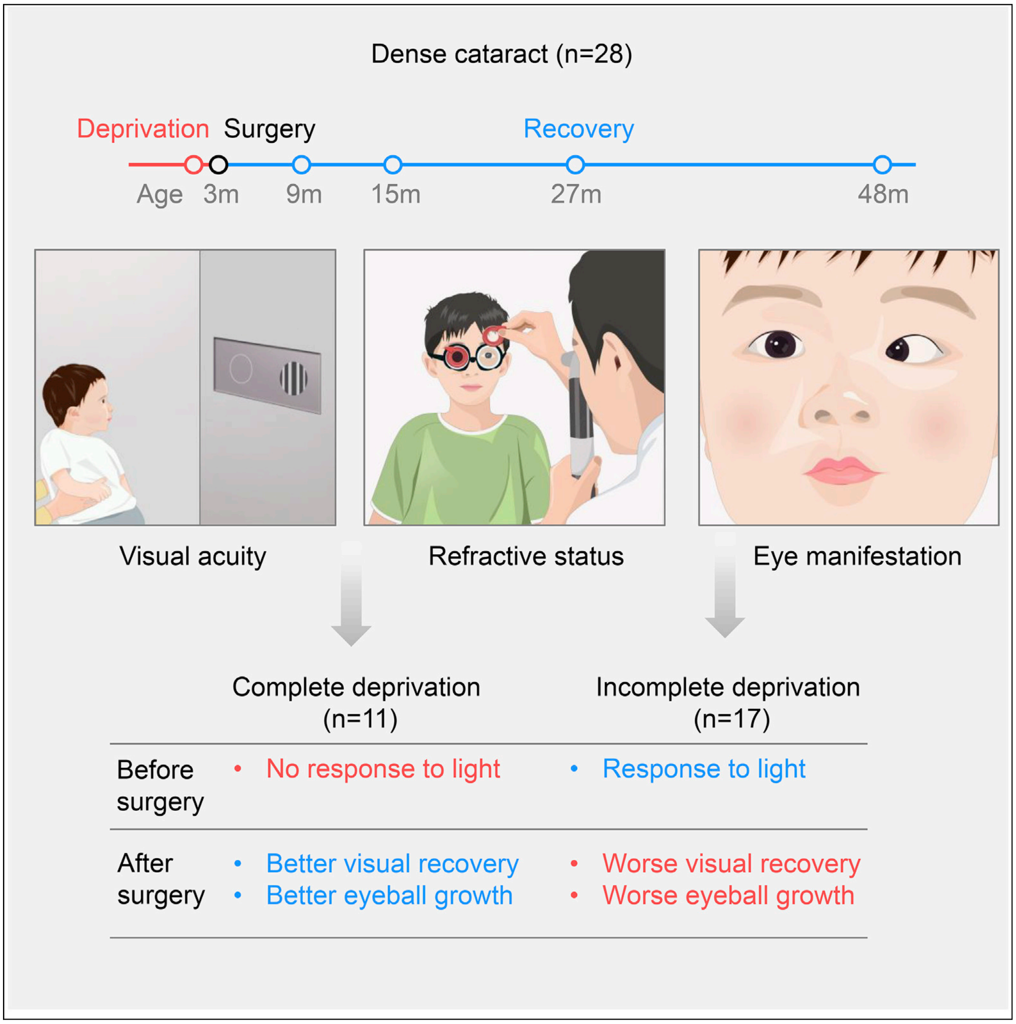
The Detrimental Effect of Noisy Visual Input on the Visual Development of Human Infants



Erping Long, Xiaoqing Gao, Yifan Xiang, ..., Yi Zhu, Chuan Chen, Haotian Lin

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HIGHLIGHTS

Infants with complete deprivation have developed better acuity than incomplete ones

Plasticity is better preserved in complete deprivation infants than in incomplete ones

Infants with complete deprivation have less myopic shift than incompletes ones

Early noisy input has the detrimental effect on human visual development

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The Detrimental Effect of Noisy Visual Input on the Visual Development of Human Infants

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SUMMARY

We followed visual development in a rare yet large sample of patients with congenital bilateral cataract for 4 years. We divided the patients into two groups: a complete deprivation group with no response to a flashlight pointing to either of their eyes and otherwise an incomplete deprivation group. All the patients received cataract surgery at age of 3 months. From 27 months onward, the complete deprivation group showed better developmental outcomes in acuity and eyeball growth than the incomplete deprivation group. Such a seemingly counterintuitive finding is consistent with research on visually deprived animals. Plasticity is better preserved in animals receiving a short period of complete visual deprivation from birth than in animals who saw diffuse light. The current finding that plasticity in visual development is better preserved in human infants with complete visual deprivation than in those who can see diffuse light but not patterned visual input has important clinical implications.

INTRODUCTION

Patterned visual input early in life has been crucial for the development of a wide range of visual functions (Maurer et al., 1999; Kalia et al., 2014). Human infants who experience transient early visual deprivation as a result of congenital cataracts have permanent deficits in visual acuity, perception of high spatial frequency information, global motion, and face perception and have abnormal patterns in multisensory integration (Chen et al., 2017; de Heering and Maurer, 2014; Gandhi et al., 2017; de Heering et al., 2016; Collignon et al., 2015). The visual system retains considerable plasticity despite the visual deprivation, as improvements in many basic visual functions are seen after restoring normal visual input. There is a substantial individual difference in the developmental outcome of early visually deprived patients (Kalia et al., 2014). What determines a patient to have a better or worse developmental outcome after receiving normal visual input is a very important question; one that not only speaks to developmental plasticity in the visual system, but also has practical implications for recovery of visual functions in early visually deprived patients.

RESULTS

To answer this question, we longitudinally followed the visual development of a large sample of patients with congenital cataract for 4 years (N = 28, details in Transparent Methods). All these patients were born with bilateral dense central cataracts, which blocked all patterned visual inputs. Importantly, although such patients cannot see any *patterned* visual input, they may still sense diffused light through their cataractous lenses. Therefore, right before the cataract surgery, we assessed their responsiveness to light using a standard light chasing procedure based on the 11th Revision of the International Classification of Diseases (ICD-11) (WHO, 2010). Based on their responsiveness to light, we divided the patients into two groups: those who failed to show any response in the light chasing procedure (complete deprivation group, N = 11) and those who did show some signs of light chasing (incomplete deprivation group, N = 17) (detailed records are tabulated in Table S1).

All the patients had their cataracts surgically removed at the age of 3 months. After surgery, the infants received spectacle lenses so visual input could be focused on their retina. As previous studies have shown that the length of visual deprivation is correlated with the final visual acuity (Bonaparte et al., 2016; Birch et al., 2009), having all the infants operated at the same age allowed us to compare the subsequent recovery process among patients. After visual input was restored, we tracked the development of their vision at the ages of 9, 15, 27, and 48 months (i.e., 6, 12, 24, and 45 months post surgery, respectively). For each visit, we measured their visual acuity with the Teller acuity card and the refractive status of their eyeballs (details in Transparent Methods).

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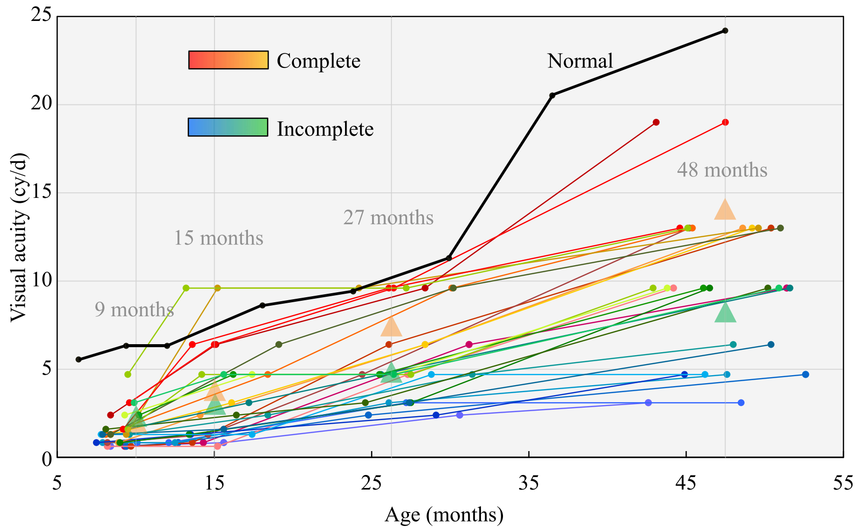

Figure 1. Development of Visual Acuity in Patients with Congenital Cataract after Restoring Visual Input

We longitudinally followed 28 patients with congenital cataract for 4 years. All these patients were born with bilateral dense central cataracts, and they received cataract surgery at 3 months of age. After surgery, we tracked the development of their vision at the ages of 9, 15, 27, and 48 months. Normal acuity values were presented as a reference (black line). The mean values for complete (yellow triangle) and incomplete (green triangle) deprivation subgroups were presented. We saw two interesting patterns. First, with age, we saw increasing variability in visual acuity among the patients. Second, when we classified these patients based on their responsiveness to light, the complete deprivation group (red and yellow curves) showed a faster improvement of visual acuity than the incomplete deprivation group (green and blue curves). Notes: cy/d = cycle/degree.

As shown in Figure 1, variability in visual acuity increased among the patients as a function of age. Interestingly, some infants developed consistently better over time than the others. Did cataract density predict recovery? Surprisingly, the better recoverers were from the complete deprivation group, who even failed to show any response to light before the cataract surgery. More specifically, as shown in Figure 2A, the two groups of infants did not differ in their visual acuity at the age of 9 months (1.32 $\pm$ 0.76 versus 1.60 $\pm$ 1.02 cy/d, $p = 0.436$) or at the age of 15 months (3.87 $\pm$ 2.88 versus 3.03 $\pm$ 2.38 cy/d, $p = 0.449$). However, a significant difference emerged at the age of 27 months (7.55 $\pm$ 1.97 versus 4.40 $\pm$ 2.10 cy/d, $p = 0.0008$). Such a difference even increased at the age of 48 months (13.47 $\pm$ 2.90 versus 7.71 $\pm$ 3.10 cy/d, $p = 8.27 \times 10^{-5}$). Therefore, from the age of 27 months onward, the infants from the complete deprivation group had substantially better recovery in visual acuity than the infants from the incomplete deprivation group. The lack of difference at the age of 9 and 15 months between the two groups could have been due to a floor effects, given that the range of visual acuity is relatively narrow.

Eyeball growth (refractive status) followed a similar pattern as for visual acuity. It has been shown that axial elongation occurs when the eye is deprived of patterned visual input in human infants as a result of eyelid closure (Hoyt et al., 1981; Liu et al., 2016; O'Leary and Millodot, 1979) as well as in animal models with visual deprivation (Wilson and Sherman, 1977; Yinon et al., 1980, Wiesel and Raviola, 1977). We identified eyeball overgrowth (also named myopic shift) as an adverse outcome with poor prognosis. As shown in Figure 2B, the complete deprivation group exhibited less overgrowth than the incomplete deprivation group at the age of 15 months (5.86 $\pm$ 1.24 versus 7.65 $\pm$ 1.92 diopters [D], $p = 0.008$), with no difference between two groups at the age of 9 months, 4.66 $\pm$ 2.69 versus 5.24 $\pm$ 2.08 D, $p = 0.571$. This difference became more pronounced with age at 27 (7.57 $\pm$ 1.59 versus 11.35 $\pm$ 2.58 D, $p = 8.81 \times 10^{-5}$) and 48 months (11.55 $\pm$ 1.75 versus 14.96 $\pm$ 1.75 D, $p = 8.84 \times 10^{-5}$).

In the current patient sample, there were six cases of nystagmus (Table S1). Five of them were from the complete deprivation group. A chi-square test or Fisher's exact test suggested a link between the occurrence of nystagmus and completeness of deprivation ($\chi^2 = 6.212$, $p = 0.013$, Table S2). There were also six cases of strabismus. Four of them were from the complete deprivation group, but the chi-square test did not reach significance ($\chi^2 = 3.187$, $p = 0.074$, Table S2). Given the small sample size and low number of occurrences of

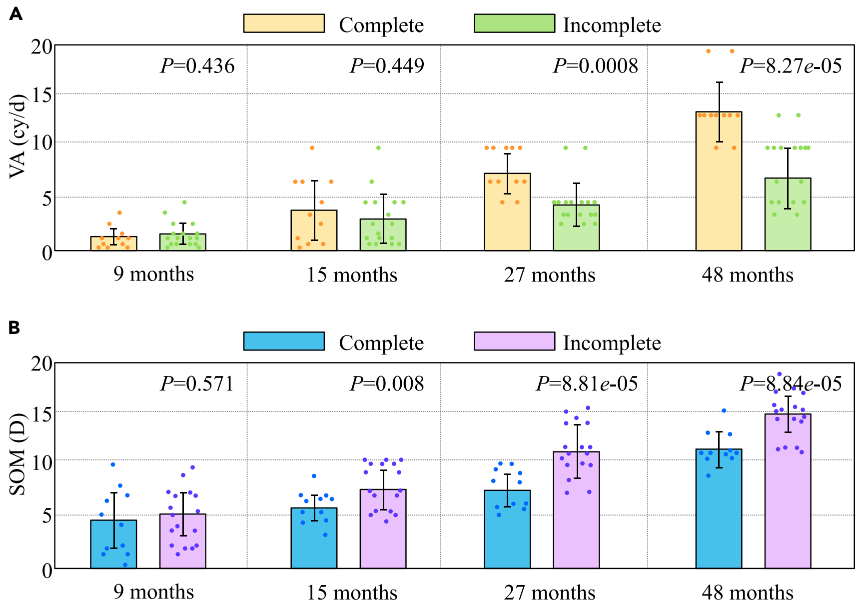

Figure 2. Comparison of Visual Acuity and Eyeball Growth between the Complete and Incomplete Deprivation Groups

(A) Based on the responsiveness to light, we classified the infants into complete deprivation or incomplete deprivation subgroups. The VA development of the complete group (n = 11, yellow bars) is significantly better than that of the incomplete group (n = 17, green bars) at the age of 27 (7.55 $\pm$ 1.97 versus 4.40 $\pm$ 2.10 cy/d, p = 0.0008) and 48 months (13.47 $\pm$ 2.90 versus 7.71 $\pm$ 3.10 cy/d, p = 8.27 $\times$ 10^{-5}) but not at the age of 9 (1.58 $\pm$ 1.14 versus 1.41 $\pm$ 0.71 cy/d, p = 0.663) and 15 months (3.87 $\pm$ 2.88 versus 3.03 $\pm$ 2.38 cy/d, p = 0.449).

(B) The structural overgrowth magnitude (SOM) has been identified as an adverse outcome (myopic shift) with poor prognosis. The SOM of the complete group (blue bars) is significantly less than that of the incomplete subgroup (purple bars) at ages 15 (5.86 $\pm$ 1.24 versus 7.65 $\pm$ 1.92 diopters (D), p = 0.008), 27 (7.57 $\pm$ 1.59 versus 11.35 $\pm$ 2.58 D, p = 8.81 $\times$ 10^{-5}), and 48 months (11.55 $\pm$ 1.75 versus 14.96 $\pm$ 1.75 D, p = 8.84 $\times$ 10^{-5}) but not at age 9 months (4.66 $\pm$ 2.69 versus 5.24 $\pm$ 2.08 D, p = 0.571). VA, visual acuity; cy/d, cycle/degree; D, diopters. All comparisons were analyzed by using the independent sample t test.

nystagmus and strabismus, we are not making any strong claim on relation between completeness of deprivation and manifestation of nystagmus and strabismus. Instead, we report the recovery results of these individuals having nystagmus and strabismus, in comparison with the others without these manifestations in Table S3.

Taken together, these results suggest a counterintuitive but consistent pattern in both functional and structural development in infants who experienced 3 months of early visual deprivation: those who were completely deprived of any visual input in the first 3 months of life had *better* outcomes up to 4 years after normal visual input was restored than those who received diffused light input.

DISCUSSION

Our findings are consistent with research on visual development in animals reared in darkness or having their eyelids sutured. Kittens reared in complete darkness for up to 4 months of age achieved normal acuity after 4 months of exposure to normal visual input (Timney et al., 1978), whereas this was not the case for kittens subjected to bilateral lid suture (Mitchell, 1988). Physiological data showed that, after prolonged dark rearing, most cells in cat visual cortex were still binocularly activated and had non-specific receptive field properties, leaving the cortex in a state that can be modified by subsequent visual experience. On the other hand, prolonged binocular suture resulted in a high proportion of unresponsive cells, as well as cells with unmappable receptive fields, and a low proportion of binocularly responsive cells (Mower et al., 1981). In addition, the cats (Cynader and Mitchell, 1980; Cynader, 1983;) and rats (Fagiolini et al., 1994; Guire et al., 1999) that received monocular deprivation with dark rearing were found to present prolonged sensitivity. As Jampolsky suggested, dark-rearing may leave a ''clean slate'' for the development of the visual cortex (Jampolsky, 1994).

The finding that complete deprivation but not diffused input may preserve plasticity for the subsequent development of visual acuity and eyeball growth has important clinical implications. For patients with congenital bilateral cataract, bilateral patching might prevent diffused light input, thereby preserving plasticity for subsequent development after normal visual input is restored. One the other hand, it is important to consider the interactions between visual development and the development of other senses. Recent studies have found abnormalities in cross-modal perception (Chen et al., 2017; de Heering et al., 2016; Collignon et al., 2015) in adults who were visually deprived early in life as a result of congenital bilateral cataracts. Such abnormality in cross-modal perception raises the possibility that the unstimulated visual cortex can be recruited by other sensory modalities. It would be important for future studies to investigate whether cross-modal recruitment is dependent on the nature of deprivation, namely, complete deprivation versus incomplete deprivation with diffused light input. Moreover, the extent of bilateral deprivation is reported to affect strabismus and nystagmus after surgery (Birch et al., 2009). It would be interesting to investigate the recovery of these eye manifestations with sufficient sample size in the future.

In summary, the current findings suggest that, in addition to *missing patterned visual input*, receiving diffused light can also have a detrimental effect on the subsequent development of vision. Preventing such diffused input (i.e., by ensuring complete deprivation) for a short period early in life may lead to a better outcome in visual development.

Limitations of the Study

Owing to the current samples, we were currently unable to have sufficient statistical power to overcome the potential floor effects in the time point of 9 and 15 months. Also, the relation between completeness of deprivation and manifestation of nystagmus and strabismus remains unclear because of the limited samples with nystagmus and strabismus.

METHODS

All methods can be found in the accompanying Transparent Methods supplemental file.

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.isci.2019.100803.

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AUTHOR CONTRIBUTIONS

E.L. designed the research; H.L., Y.X., Z.L., A.X., X.H., Y. Zhang, and E.L. collected the data; Y.X., A.X., X.H., Y. Zhang, and E.L. conducted the study; E.L. analyzed the data; E.L. and X.G. co-wrote the manuscript; H.L., X.G., Z.L., Y. Zhu, C.C., and E.L. critically revised the manuscript; and all the authors discussed the results and provided comments regarding the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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Supplemental Information

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SUPPLEMENTARY INFORMATION

TRANSPARENT METHODS

Study population. A total of 28 individuals registered with the Childhood Cataract Program of the Chinese Ministry of Health (CCPMOH) were recruited between January 2012 and December 2013 from Zhongshan Ophthalmic Center (ZOC), one of the largest eye hospitals in China (Lin, et al, 2015). These participants were born with bilateral dense central cataracts and underwent surgery for bilateral cataract removal at 3 months old. A total of 13 infants (46.42%, 13/28 were male. Apart from their history of cataracts, all individuals were healthy (e.g., no metabolic diseases, mental retardation or central nervous diseases) and had no history of inherited diseases. All infants underwent complete follow-up during the 4 year period post-surgery. The cataract type, density and location was examined using the slit lamp–adapted anterior segmental photography (BX900; Haag-Streit AG, Koniz, Switzerland). All diagnostic criteria, including eye manifestations (light chasing, strabismus, and nystagmus) were based on the 11th Revision of the International Classification of Diseases (ICD-11). Specifically, for light chasing, we shined a penlight into the infant's eye at distance of 50 centimeter to test whether the infants responded to and chased the light in at least 1 quadrants (9 quadrants were tried). We conducted the right eye first and then the left eye.

Ethnical approval. The research protocol was for exploratory purposes and was approved by the Institutional Review Board/Ethics Committee of Sun Yat-sen University (Guangzhou, China). Informed written consent was obtained from at least one family member of each participating child, and the tenets of the Declaration of Helsinki were followed throughout the study. This study was registered with ClinicalTrials.gov (Identifier: NCT03593824).

Functional traits of visual grating acuity. All monocular best corrected visual grating acuities were measured using a complete set of Teller Visual Cards (Stereo Optical Company, Inc., IL, USA) (Ciocler et al, 2013). The set consisted of 15 cards with gratings ranging in spatial frequency from 0.32 to 38 cycles/cm in half-octave steps as well as a low vision card and a blank grey card. Luminance was kept above 10 candela/m^2 by utilizing overhead diffused fluorescent lighting and a spotlight directed towards the ceiling. In addition, the contrast in the cards was approximately 60–70%. The order of testing eyes (right/left) was randomized. Each type of examination was conducted by a single experienced examiner who was blind to the results of previous assessments. Normal acuity values were used as a reference based on the previous study (Mayer et al, 1995).

Structural traits of refractive status. All examinations of refractive status were conducted using the NVision-K 5001 autorefractor (Shin Nippon, Rexxam, Japan) and were confirmed with objective retinoscopy. The order of testing eyes (right/left) was randomized. Three refractive error measurements were taken for each eye, and the mean result was recorded. The spherical equivalent power was included in the final analysis by adding half of the cylinder power to the sphere power.

Statistical analysis. The right eye was chosen for each individual. The data were presented as the mean ± standard deviation (SD). An independent sample t-test was used to compare the differences in functional and structural development magnitude between the complete deprivation and incomplete deprivation groups. All the statistical tests were two-tailed, and a P value below 0.05 was considered statistically significant. Analyses were implemented using the statistical software R, version 3.4.2 (R Project for Statistical Computing, Vienna, Austria).

Table S1. Information of the complete and incomplete deprivation groups, related to Figure 1.

Identifier	Group	Strabismus	Nystagmus	No light chasing	VA (48m, bilateral)	VA for both eyes (48m, right/left)
1	**C**	**Y**	**Y**	**Y**	**9.6**	**6.4/6.4**
2	**I**	/	/	/	**3.1**	**3.1/3.1**
3	**C**	/	**Y**	**Y**	**9.6**	**6.4/9.6**
4	**I**	/	/	/	**4.7**	**3.1/4.7**
5	**C**	/	/	**Y**	**13**	**9.6/9.6**
6	**I**	/	/	/	**3.1**	**3.1/2.4**
7	**I**	/	/	/	**4.7**	**4.7/3.1**
8	**C**	/	**Y**	**Y**	**13**	**9.6/13**
9	**I**	/	/	/	**4.7**	**4.7/4.7**
10	**C**	/	/	**Y**	**13**	**13/9.6**
11	**I**	/	/	/	**9.6**	**9.6/6.4**
12	**C**	/	/	**Y**	**13**	**9.6/9.6**
13	**C**	**Y**	**Y**	**Y**	**13**	**9.6/9.6**
14	**I**	/	/	/	**4.7**	**4.7/4.7**
15	**I**	/	/	/	**6.4**	**4.7/6.4**
16	**I**	**Y**	/	/	**13**	**9.6/9.6**
17	**I**	/	/	/	**6.4**	**6.4/4.7**
18	**C**	/	/	**Y**	**13**	**9.6/9.6**
19	**I**	/	/	/	**9.6**	**6.4/6.4**
20	**I**	/	/	/	**9.6**	**6.4/9.6**
21	**C**	**Y**	**Y**	**Y**	**13**	**13/9.6**
22	**I**	/	/	/	**9.6**	**9.6/9.6**
23	**C**	**Y**	**Y**	**Y**	**19**	**13/13**
24	**I**	/	/	**Y**	**19**	**19/13**
25	**I**	/	/	/	**9.6**	**6.4/6.4**
26	**I**	/	/	/	**9.6**	**9.6/6.4**
27	**I**	**Y**	/	/	**13**	**9.6/9.6**
28	**I**	/	/	/	**9.6**	**6.4/6.4**

Footnotes: Based on their responsiveness to light before the cataract surgery, we classified the patients into complete (C, n = 11) or incomplete (I, n = 17) deprivation groups. VA=visual acuity (cycle/degree); m=months.

Table S2. The statistical tests on link between the occurrence of nystagmus and completeness of deprivation, related to Figure 2.

		Nystagmus		
		Yes	No	Total
Light chasing	Yes	1	16	17
	No	5	6	11
	Total	6	22	28
χ^2= 6.212, *P*=0.013				

		Strabismus		
		Yes	No	Total
Light chasing	Yes	2	16	17
	No	4	6	11
	Total	6	22	28
χ^2= 3.187, *P*=0.074				

Notes: The chi-squared test or Fisher's exact test (when more than one-fifth of cells' theoretical frequency is greater than five in the contingency tables) was employed to investigate the link between the occurrence of nystagmus/strabismus and completeness of deprivation.

Table S3. The outcomes of infants with preoperative strabismus and nystagmus, related to Figure 2.

	VA							
	9 month		**15 month**		**27 month**		**48 month**	
Strabismus	**Yes (n=6)**	**No (n=22)**	**Yes (n=6)**	**No (n=22)**	**Yes (n=6)**	**No (n=22)**	**Yes (n=6)**	**No (n=22)**
Mean	**1.99**	**1.36**	**5.69**	**2.73**	**8.78**	**4.78**	**13.43**	**9.03**
SD	**1.32**	**0.74**	**2.69**	**2.21**	**1.83**	**2.00**	**2.78**	**3.93**
P	**0.34**		**0.06**		**0.002**		**0.01**	

	VA							
	9 month		**15 month**		**27 month**		**48 month**	
Nystagmus	**Yes (n=6)**	**No (n=22)**	**Yes (n=6)**	**No (n=22)**	**Yes (n=6)**	**No (n=22)**	**Yes (n=6)**	**No (n=22)**
Mean	**1.23**	**1.56**	**3.38**	**3.36**	**7.43**	**5.15**	**12.9**	**9.18**
SD	**0.63**	**0.99**	**2.53**	**2.65**	**2.24**	**2.42**	**3.14**	**4.02**
P	**0.37**		**0.99**		**0.08**		**0.05**	

	SOM							
	9 month		**15 month**		**27 month**		**48 month**	
Strabismus	**Yes (n=6)**	**No (n=22)**	**Yes (n=6)**	**No (n=22)**	**Yes (n=6)**	**No (n=22)**	**Yes (n=6)**	**No (n=22)**
Mean	**4.33**	**5.35**	**5.75**	**7.27**	**7.46**	**10.5**	**10.42**	**14.49**
SD	**2.91**	**2.08**	**1.98**	**1.74**	**2.03**	**2.78**	**0.95**	**1.92**
P	**0.49**		**0.16**		**0.02**		**4.5e-06**	

	SOM							
	9 month		**15 month**		**27 month**		**48 month**	
Nystagmus	**Yes (n=6)**	**No (n=22)**	**Yes (n=6)**	**No (n=22)**	**Yes (n=6)**	**No (n=22)**	**Yes (n=6)**	**No (n=22)**
Mean	**4.50**	**5.30**	**5.96**	**7.22**	**7.46**	**10.52**	**11.38**	**14.23**
SD	**2.86**	**2.12**	**1.99**	**1.78**	**1.91**	**2.78**	**1.89**	**2.17**
P	**0.58**		**0.24**		**0.01**		**0.02**	

Notes: VA = visual acuity; SOM = structural overgrowth magnitude; SD = standard deviation; All comparisons were analyzed by using the independent sample t-test.

SUPPLEMENTARY REFERNCES

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