Development of pattern vision following early and extended blindness

Amy Kalia[a,1,2], Luis Andres Lesmes[b,c,1], Michael Dorr[b], Tapan Gandhi[a,d], Garga Chatterjee[a], Suma Ganesh[e], Peter J. Bex[b], and Pawan Sinha[a]

[a]Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139; [b]Schepens Eye Research Institute, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA 02114; [c]Adaptive Sensory Technology, Boston, MA 02114; [d]Defence Institute of Physiology and Allied Sciences, Government of India, New Delhi 110016, India; and [e]Department of Pediatric Ophthalmology, Dr. Shroff's Charity Eye Hospital, Daryaganj, New Delhi 110002, India

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Visual plasticity peaks during early critical periods of normal visual development. Studies in animals and humans provide converging evidence that gains in visual function are minimal and deficits are most severe when visual deprivation persists beyond the critical period. Here we demonstrate visual development in a unique sample of patients who experienced extended early-onset blindness (beginning before 1 y of age and lasting 8–17 y) before removal of bilateral cataracts. These patients show surprising improvements in contrast sensitivity, an assay of basic spatial vision. We find that contrast sensitivity development is independent of the age of sight onset and that individual rates of improvement can exceed those exhibited by normally developing infants. These results reveal that the visual system can retain considerable plasticity, even after early blindness that extends beyond critical periods.

brain plasticity | sensitive periods | sight restoration | visual impairment | childhood blindness

Early visual experience is crucial to the normal development of the neural substrates of vision. Abnormal early experience results in dramatic changes in visual cortices, as well as corresponding behavioral deficits in visual abilities (1–7). Neurophysiological studies in animals following early binocular visual deprivation demonstrate reductions in the responsiveness, orientation selectivity, resolution, and contrast sensitivity of neurons in visual cortex (1–4) that persist when sight is restored later in life (8). Given their vulnerability to deprivation, can these neural mechanisms recover functionality after extended periods of deprivation?

To investigate this question, we examined the development of contrast sensitivity in a unique group of sight restoration patients. Contrast sensitivity is a fundamental metric of visual performance that describes the sensitivity of neurons and observers. It is the primary visual limitation in a variety of tasks, including mobility, reading, and face and object recognition (9). The neural underpinnings of contrast sensitivity are found in early visual cortex (10–12). In both brain and behavior, contrast sensitivity functions (CSFs) exhibit a characteristic shape: a band-pass function with peak contrast sensitivity and a falloff at relatively lower and higher spatial frequencies. There is a direct relationship between behavioral and neural contrast sensitivity: the peak frequency of behavioral contrast sensitivity is the mode of the distribution of peak frequencies of neural CSFs (12). Contrast sensitivity therefore provides a valuable assay for visual development (3) and examination of its change following deprivation can provide fundamental insights into the critical periods of neural plasticity.

Two factors are thought to influence the extent of visual ability after blindness: the age of onset and the duration of blindness. We define "early-onset" blindness as occurring before 1 y of age. We define "extended" blindness as lasting at least until early childhood, when many visual abilities in normally developing children reach adult levels. Contrast sensitivity in particular develops until approximately age 7 in normally sighted humans (13–15). Previous studies of sight restoration in humans have examined patients after either early-onset blindness or extended blindness, but not with both. Following early-onset blindness lasting a short duration (from birth to 6 mo of age), contrast sensitivity is deficient at high spatial frequencies and does not improve after age 7 (16). Improvement in contrast sensitivity is even more limited after extended blindness with delayed onset. In Fine et al.'s study (17), patient MM, blind from age 3 to 43, did not exhibit contrast sensitivity improvement for the 2 y following sight restoration surgery. He has continued to exhibit impaired vision and an abnormal receptive field map in V1 with reduced foveal representation and increased receptive field sizes (18). These findings suggest that the neural mechanisms supporting contrast sensitivity only develop during a specific age-defined window and cannot develop if the period of binocular deprivation extends beyond this window. Without exposure to the normal range of spatial frequency information, these neural substrates may lose plasticity after critical periods of development have passed.

Contrary to these predictions, we report marked improvements in the CSFs of a unique sample of sight restoration patients who experienced early-onset visual deprivation that remained untreated for an extended duration (the minimum age at treatment was 8 y). These patients exhibited extremely poor presurgical acuity of, at most, finger counting at a distance of 1 m. According to the standards adopted by the World Health Organization (19), this level of vision is equivalent to an acuity of 20/1,200 (1/60) and is categorized as the third most severe level of

Significance

Deprivation of vision during typical age-defined critical periods results in seemingly irreversible changes in neural organization and behavior in animals and humans. We describe visual development in a unique population of patients who were blind during typical critical periods before removal of bilateral cataracts. The rarity of such cases has previously limited empirical investigations of this issue. Surprisingly, we find substantial improvement after sight onset in contrast sensitivity, a basic visual function that has well-understood neural underpinnings. Our results show that the human visual system can retain plasticity beyond critical periods, even after early and extended blindness.

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Conflict of interest statement: L.A.L., P.J.B., and M.D. declare intellectual property interest in contrast sensitivity testing (US 7,938,538 and US 61/644,889), and equity interest in a venture, Adaptive Sensory Technology, to commercialize such testing.

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[1]A.K. and L.A.L. contributed equally to this work.

[2]To whom correspondence should be addressed. E-mail: akalia@mit.edu.

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blindness (after light perception and no light perception). This study was conducted as part of Project Prakash, a joint scientific and humanitarian effort to treat curable blindness in India and to investigate the resulting course of visual development (20). Access to this population allowed us to examine contrast sensitivity across a large sample of sight restoration patients compared with previous reports (16–18, 21–23). Consequently, we could also explore individual differences in contrast sensitivity development.

Results

Longitudinal CSF Assessment. To determine whether the neural mechanisms supporting contrast sensitivity develop with exposure to patterned images following deprivation, we compared two postsurgical assessments of contrast sensitivity, measured 6 mo apart in 11 subjects. For each individual subject, Fig. 1 presents longitudinal assessments of contrast sensitivity across a range of postsurgical periods: the first assessment occurred between 1 wk and 26 mo after surgery. Table S1 describes additional subject characteristics (including surgical age, presurgery acuity, and the postsurgical period of assessment, presented in each square in Fig. 1). Five subjects (*Upper* row), from ages 11 to 15, demonstrate significant contrast sensitivity improvements. Two subjects (S2 and S3) show remarkable improvements of 1.5 log units in contrast threshold (30× improvement) relative to the first postsurgical assessment. For one subject (S11, *Lower* row, *Far Right*), an observed decrease in contrast sensitivity was likely due to a mild posterior capsular opacification, or "secondary cataract," which is a common complication after cataract surgery (25).

We quantified the amount of CSF improvement by computing the change in the area under the log CSF (AULCSF) between the first and second postsurgery CSFs. The AULCSF provides a simple, broad metric for the total gain in contrast sensitivity, including gains in sensitivity (upward curve shifts) and gains in spatial frequency (rightward curve shifts). This metric avoids underestimating general improvements that may not be captured by measures of peak spatial frequency or resolution acuity. Notably, patient S2 exhibits the largest increase in AULCSF (1.0). Despite very poor performance immediately after surgery, peak contrast detection threshold improved from 50% to less than 1%. The gains in contrast sensitivity exhibited by five subjects demonstrate that the human visual system is capable of developing significant function in late childhood and adolescence following early-onset blindness.

Short-Term Visual Improvement. In a subsample of patients ($n = 3$), we evaluated the potential optical contributions to visual improvements by comparing contrast sensitivity assessed before surgery with repeated assessments in the few weeks after surgery. The surgical removal of opaque lenses allowed fine spatial details to be resolved on the retinas for the first time. If this information was perceived immediately after cataract removal, it suggests that partial development occurred in postoptical stages of the visual pathway despite the absence of visual input. In Fig. 2, S1 and S6 exhibit significant contrast sensitivity improvement immediately after surgery. Similarly, S2 was unable to perceive any of the stimuli correctly before surgery, but after surgery could identify several stimuli correctly. It is notable that, besides the short-term improvements demonstrated in the first postsurgical weeks by all subjects, S2 continued to improve in the months following surgery. This indicates that optical improvement from cataract removal cannot account for the full extent of this visual development. There is previous neuroanatomical evidence that retinal morphology, in terms of cell number and size, and the spatial and temporal selectivity of neurons in lateral geniculate nucleus are unaffected by visual deprivation (26, 27). More recent studies show that retinal changes following sight restoration occur rapidly; cone realignment after cataract removal occurs in the first 10 days after surgery (28). Although it is difficult to link anatomical and behavioral changes, these findings are in general agreement with the time course of optical changes seen in Fig. 2. Identifying the immediate contribution of the lens removal suggests that the improvements in contrast sensitivity observed over longer postsurgical periods (5–30 mo; Fig. 1) cannot be fully explained by changes in the precortical visual pathway.

Individual Variability in Development. To identify sources of variability in contrast sensitivity development, we examined the observed changes in AULCSF with respect to four factors: age at surgery, time since surgery, presurgery acuity, and type of cataract. None of these factors exhibited significant relationships ($P > 0.05$) with change in AULCSF (Fig. 3) as demonstrated by tests of correlation (age at surgery) and Kruskal–Wallis one-way analyses of variance by ranks (time since surgery, presurgical acuity, and type of cataract). Interestingly, the amount of visual improvement was independent of the age of subjects at treatment.

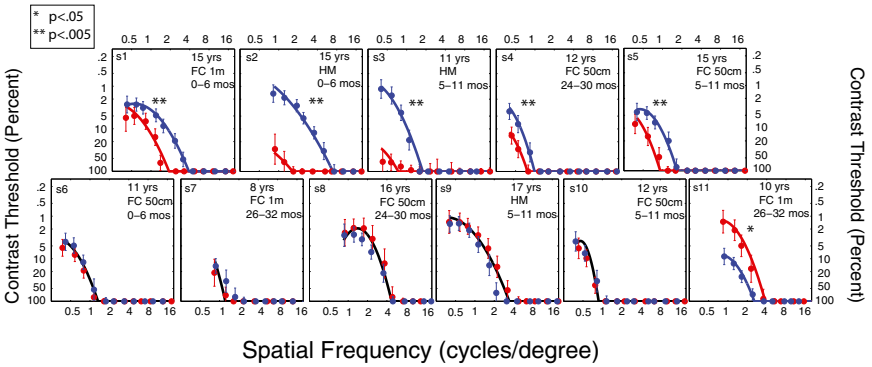

Fig. 1. Longitudinal contrast sensitivity assessment. Contrast sensitivity was assessed over 6 mo following removal of bilateral congenital cataracts. Raw sensitivity estimates obtained at first and second assessments are presented (red and blue dots, respectively), with error bars representing 65% confidence intervals. For each observer, the text within each box presents the patient's age at surgery, preoperative acuity (FC, finger counting at the specified distance; HM, hand movements), and the postsurgical time period corresponding to the CSF assessment (0 indicates the first week after surgery). Curve fits (red, blue, and black lines) of contrast sensitivity functions (CSFs) represent nested-model hypothesis testing (24) that considers whether contrast sensitivity in the first and second assessments are significantly different (red and blue, $*P < 0.05$, $**P < 0.005$) or not (black). In the former case, the contrast sensitivity data are jointly fit according to models of contrast sensitivity change across assessments (e.g., change in peak threshold or peak frequency). Five of 11 patients (*Upper* row) exhibit significant contrast sensitivity development, with two demonstrating a substantial (>30 times) improvement in their peak contrast thresholds.

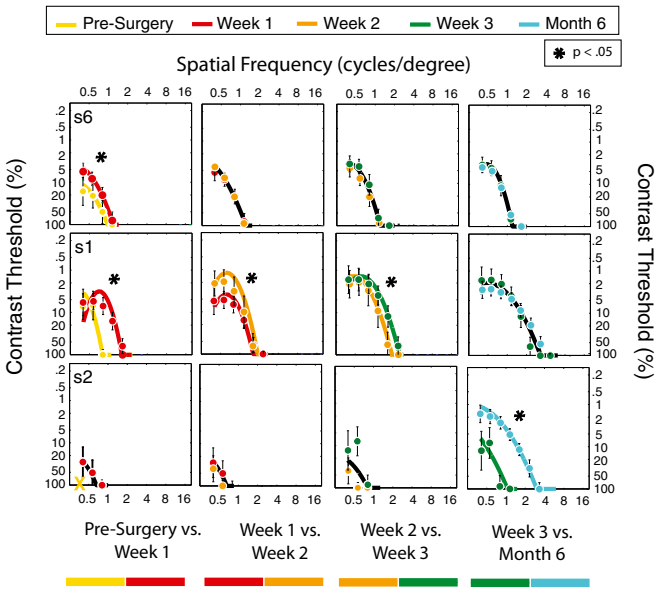

Fig. 2. Short-term contrast sensitivity assessment. For three patients (one in each row), contrast sensitivity was evaluated over a finer schedule: pre-surgery, 1, 2, and 3 wk after surgery, and 6 mo after surgery. Contrast sensitivity estimates (dots) obtained from successive assessments (e.g., pre-surgery vs. week 1) are compared, with error bars representing 65% confidence intervals. No change in contrast sensitivity between successsive assessments is indicated by a single function (black). Significant changes in contrast sensitivity (*$P < 0.05$) are accounted for with distinct functions. The different time course of improvements across patients, in the weeks following surgery, suggests that visual improvements reflect contributions of both optical factors (lens opacity removal) and neural development.

Comparison with Normal Development. The observed improvements in some of our subjects are especially surprising because contrast sensitivity no longer improves in normally developing individuals of the same biological age (Fig. 4, *Left*) (13–15). Furthermore, two subjects even exceed the rate of development exhibited by infants (Fig. 4, *Right*) (15, 29, 30). This accelerated development is comparable to the rates at which visually deprived kittens acquire some visuomotor abilities (31). Additionally, numerous studies demonstrate adult visual plasticity from video-game playing (32–36), but the resulting gains in contrast sensitivity are not as large as the improvements shown by some of our subjects (35, 36). Although individual differences have been observed in normal development (37), little is known about the reasons for their manifestation. Despite large individual variability in our patients, these results indicate that the neural mechanisms underlying the development of contrast sensitivity are capable of accelerated growth following the delayed onset of visual information.

Cross-Sectional Survey of Contrast Sensitivity. Fig. 5 presents a broader survey of contrast sensitivity, measured in a relatively large number of sight restoration patients in Project Prakash. The range of CSFs comprises three nonoverlapping groups of subjects coded by color: patients before cataract surgery (red; $n = 8$), patients after cataract surgery (blue; $n = 18$, tests ranging from postsurgical periods of 6 mo to 5 y), and age-matched controls with normal vision (gray; $n = 28$). This figure demonstrates highly variable outcomes across individuals, but also a substantial systematic difference between pre- and postsurgery CSFs. A subset of subjects exhibits high peak contrast sensitivity (thresholds less than 2%), but the peaks are shifted to low spatial frequencies. Although there are still substantial deficits in postsurgical CSFs relative to normal vision, most subjects are able to perceive spatial frequencies that were unresolvable before surgery. The fact that contrast sensitivity functions are measurable in this population after early and extended blindness provides further evidence of preserved functionality despite severely impoverished visual stimulation for many years.

Discussion

In summary, we find substantial CSF development after early-onset and extended blindness. This development progresses over time in some subjects, with improvements occurring even a year after surgery in one patient. These improvements likely reflect cortical rather than precortical changes spurred by newly acquired visual experience. Previous studies have shown that individuals with amblyopia can exhibit improvements in basic visual abilities, such as acuity and contrast sensitivity, after extensive training on challenging visual tasks requiring at least 10 sessions and often thousands of trials (38–40). Given the limited amount of time our subjects spent performing the contrast sensitivity test (30 trials per session for two to four sessions spread over 6 mo), it seems unlikely that perceptual learning could account for our results.

Our findings corroborate studies in animals, demonstrating that visual development is experience dependent; critical periods can be extended through delayed exposure to light (41, 42). More recent studies show that artificial manipulation of the molecular mechanisms of plasticity can accelerate or delay critical periods (43, 44). The onset of critical periods is linked to the maturation of GABA-modulated inhibitory circuits, a process that is triggered by visual experience. Reducing GABA function (such as by dark rearing) delays maturation of inhibitory circuits and consequently delays the onset of the critical period. Importantly, these studies were primarily conducted in rodents undergoing monocular deprivation. The longitudinal development of contrast sensitivity in our patients supports the possibility that similar mechanisms may be responsible for visual plasticity in humans.

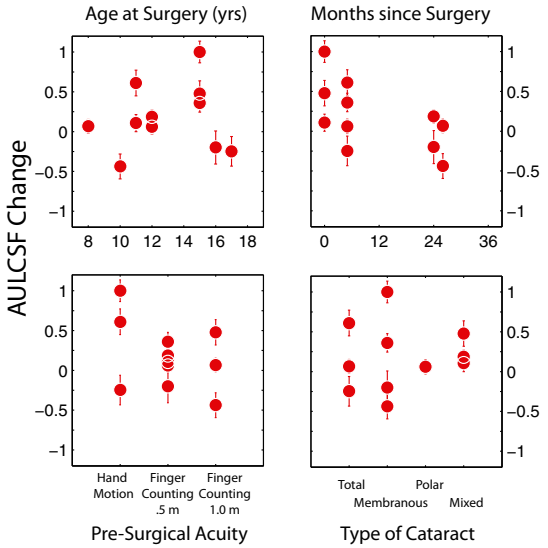

Fig. 3. Potential contributions to visual improvements. The magnitude of contrast sensitivity development, via the change in area under the log contrast sensitivity function (AULCSF), is considered as a function of four factors: age at surgery, months since surgery, presurgery acuity (FC, finger counting at the specified distance; HM, hand movement), and the type of cataract ("mixed" indicates that the subject had different types of cataract in each eye). None of the four factors showed significant relationships ($P > 0.05$) with observed AULCSF changes.

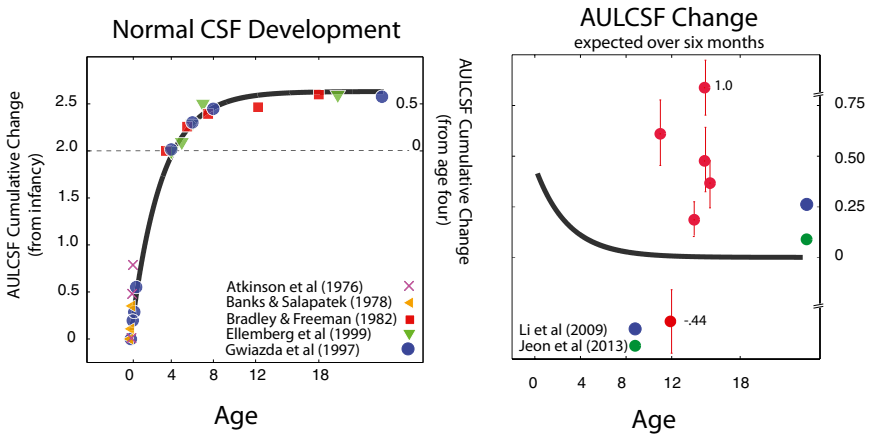

Fig. 4. Normal contrast sensitivity development. (*Left*) To summarize and compare previous studies of infant and childhood contrast sensitivity development, we normalized the AULCSF values reported for different ages to the earliest AULCSF obtained in each study: either 1–2 mo or 4 y old. For normal development, the change in AULCSF from 2 to 8 mo is approximately the same as from 4 y to maturity. (*Right*) For reference, the pattern of normal development can be used to predict how much AULCSF change is expected over 6 mo, as a function of age (black line). For the six patients who showed significant contrast sensitivity change in Fig. 1, AULCSF changes are plotted as a function of age at surgery (red dots). To compare with other demonstrations of adult visual plasticity, AULCSF changes due to video-game playing are presented (blue and green dots) (35, 36).

This study exemplifies the remarkable capacity of the human visual system to gain functionality after early-onset, long-term deprivation. The nature of our patient pool allows us to separate the timeline of development from the age of the patients; in normally developing children, the improvement in contrast sensitivity until age 7 may be a result of visual experience rather than the person's biological age. This study thereby demonstrates an expanded window of plasticity following blindness that exceeds the age of normal contrast sensitivity development. It is unclear what accounts for the resiliency of the neural mechanisms underlying these improvements despite such extended deprivation. Another key challenge for future studies is to identify factors responsible for the variability in plasticity; some of the most obvious factors, such as age at treatment, time since surgery, or presurgical acuity, do not correlate with improvements in CSF. Similarly, in the domain of audition, early deaf patients have unexplained variable outcomes after cochlear implants (45). Notwithstanding this variability, the overarching commonality across most of our study participants is the improvement in form vision after sight onset late in childhood. This, we believe, attests to the availability of neural plasticity well into life, and, from an applied perspective, provides an optimistic prognosis for treatments of the many curably blind children in the developing world who have hitherto languished without medical care.

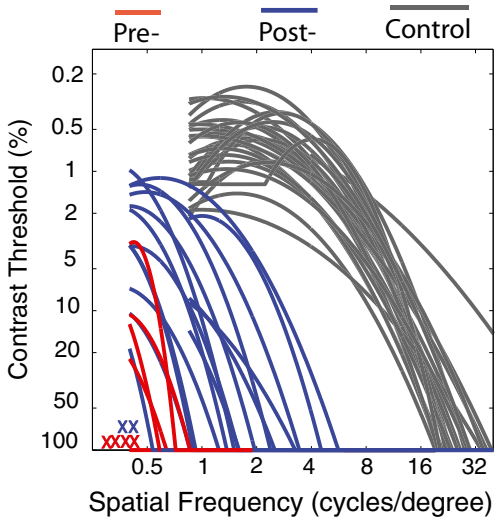

Fig. 5. Survey of contrast sensitivity. A cross-sectional evaluation of Project Prakash patients compares contrast sensitivity assessed before surgery (red) and 6 mo to 5 y after surgery (blue). CSFs of age-matched normally sighted subjects are also shown (gray). Patients who did not have measurable CSFs at the time of testing are marked with an "x." Contrast sensitivity development, and a general improvement in pattern vision, is evident with sight onset, although outcomes are variable across this unique sample.

Materials and Methods

All subjects were implanted with an intraocular lens during surgery and were prescribed the best refractive correction after surgery. Binocular vision of patients was tested with an iPad implementation of the quick CSF method (46). The quick CSF algorithm applied a Bayesian adaptive method to estimate the full shape of the CSF, via a posterior probability distribution defined over four CSF parameters (peak contrast sensitivity, peak spatial frequency, bandwidth at half-peak sensitivity, and low spatial frequency truncation) (47). CSF assessment was achieved with 30 trials, which corresponded to a test time of approximately 5 min. The test stimuli were band-pass filtered Lea symbols with peak spatial frequencies ranging from 0.5 to 24 cycles per degree, depending on the viewing distance of either 40 or 85 cm. Viewing distance remained consistent for a given patient across test sessions. We also tested normally sighted individuals between the ages of 8 and 18.

The quick CSF provides estimates of AULCSF and sensitivity (and their uncertainty) at different spatial frequencies, via the four-dimensional Bayesian posterior. To estimate the central tendency and error for contrast sensitivities from short adaptive CSF runs (Figs. 1 and 2), we used Monte Carlo sampling of the Bayesian posterior. Because each sample corresponds to one CSF—a set of contrast sensitivity estimates across spatial frequencies—Monte Carlo sampling generates distributions of contrast sensitivities defined at different spatial frequencies, which can be summarized by their median and SD. These contrast sensitivity estimates are plotted in Figs. 1 and 2. To estimate AULCSF change and its error, we similarly sampled the posteriors of the two quick CSF runs to be compared. Taking the pairwise difference of the AULCSF values corresponding to different Monte Carlo samples generates a distribution of AULCSF change. Estimates of AULCSF change and its error are presented in Figs. 3 and 4 and Table S1.

For a finer analysis of patterns of contrast sensitivity development, we used a nested model analysis to evaluate different patterns of CSF change (24). The trial-by-trial data from different quick CSF runs were fit by a maximum-likelihood analysis, and nested models were compared via log-likelihood ratio testing. A χ^2 test was applied to determine if the observed sensitivity differences were statistically significant. The candidate models of CSF development were represented by changes in (*i*) peak sensitivity, (*ii*) peak frequency, (*iii*) bandwidth, or (*iv*) their combination. The full model posits

that two unique CSFs are needed to describe pre- and postsurgical contrast sensitivity in each subject. The most reduced (null) model suggests that both conditions can be described by the same contrast sensitivity function. For six subjects shown in Fig. 1, these functions were significantly different (full vs. null model, $P < 0.05$). Three subjects (S2–S4) demonstrated improved peak sensitivity, two subjects (S1 and S5) demonstrated improved peak frequency, and one subject (S11) demonstrated reduction in peak contrast sensitivity. Finally, an analysis of CSF change in age-matched normally sighted subjects exhibited no statistical improvements in CSF over the course of 1 y (Fig. S1), attesting to the reliability of our analysis.

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