Rapid Improvement in the Acuity of Infants After Visual Input

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Visual acuity was assessed in 28 human infants who had been deprived of all patterned visual input by cataracts in one or both eyes until they were treated at 1 week to 9 months of age. Immediately after treatment, acuity was no better than that of normal newborns. Acuity improved significantly over the next month, with some improvement apparent after as little as 1 hour of visual input. Unlike findings at older ages, the pattern of results was the same for eyes treated for monocular and for binocular deprivation. The results indicate that patterned visual input is necessary for the postnatal improvement of human visual acuity and that the onset of such input initiates rapid functional development.

No matter how it is measured, visual acuity is poor at birth: The smallest stripes to which newborns respond are about 40 times larger than what can be resolved by adults with normal vision (*1–6*). There is at least a fivefold improvement in acuity by 6 months of age, although it takes several more years for acuity to reach adult levels (*2, 4, 6*). We assessed the contributions of intrinsic factors versus postnatal visual experience to this rapid postnatal improvement in acuity. We compared the grating acuity of infants who had been deprived of patterned visual input by dense central cataracts in one ($n = 16$) or both eyes ($n = 12$) to that of age-matched normal infants (*7*).

Patients had been deprived of patterned visual input for 1 week to 9 months after birth (mean, 3.7 months). Treatment involved surgical removal of the cataractous lens, leaving the eye with no means to focus images. A few days to a few weeks after surgery, the treated eyes were given appropriate contact lenses so that, for the first time, visual input was focused on the retina (*8*). We compared the monocular acuity of each eye immediately after contact lens insertion (within 10 min, that is, before significant visual input) to that of an infant of the same age who had received normal postnatal visual experience (*9*). We retested acuity after 1 hour of visual input, 1 week later, and 1 month later. We retested after such short intervals because in kittens that have been visually deprived, the onset of patterned visual input induces cortical changes after as little as 30 to 60 min (*10*) and improvement in visual acuity within a few hours (*11*).

Figure 1 shows the results immediately after contact lens insertion for patients and for age-matched normals (*12*). Whether the deprivation had been binocular or monocular, the initial acuity of treated eyes was significantly worse than the acuity of the age-matched controls and significantly worse than that of groups of normal infants tested under similar conditions (*13*) (all P's $<$ 0.0001, one-tailed paired t tests). Although there is some scatter in the data across individual infants, there is no sign of postnatal improvement before patterned visual input and each of the geometric means for patients falls between 30 and 60 min of arc, the range typically reported for normal newborns (*1–3, 5*). The acuity of patients falls farther below that of the age-matched normals, the later during the first year that they were treated (filled symbols in Fig. 2). Pearson correlations showed significant relations (all P's $<$ 0.05) between the age at contact lens insertion and the size of the deficit in the treated eye relative to its age-matched normal in patients treated for unilateral congenital cataract and each eye of patients treated for bilateral congenital cataract (r's $= 0.58$ to 0.60). The acuity in the nondeprived eye of unilateral cases (Fig. 1D) was significantly better than the acuity in the deprived eye ($P = 0.0002$, one-tailed paired t test) and did not differ from that of the age-matched normals ($P > 0.05$, two-tailed paired t test). The acuity of the nondeprived eye was higher, the later during the first year it was tested ($r = 0.77$, $P = 0.0005$).

Figure 3 shows the mean change in the acuity of patients from its initial value after each of the test intervals and the mean change in age-matched normals retested after the same intervals. Treated eyes showed significant improvements that averaged around 0.40 octaves between the immediate and 1-hour tests (arrows in Fig. 2; all P's < 0.05, one-tailed paired t tests) and around 0.60 octaves between the 1-hour and 1-month tests (all P's < 0.02). The deficit in each treated eye compared with the age-matched normal decreased from an average of just over 2 octaves on the immediate test to a mean of

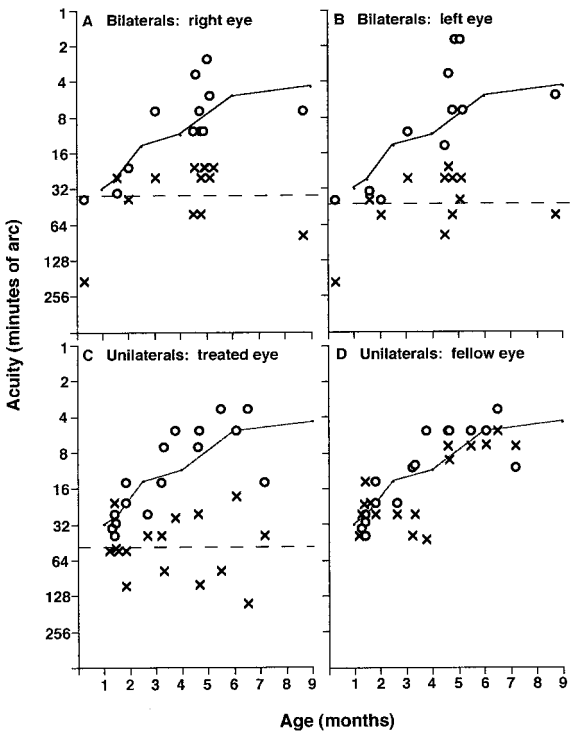

Fig. 1. Acuity on the immediate test. The *x* axis indicates the age at the time of the test, which for the treated eyes of patients is also the age at the time of the first patterned visual input. The *y* axis indicates the size (in minutes of arc) of the smallest stripes to which the eye responded. The solid line gives mean normative values for monocular tests with Teller Acuity Cards (*13*). Each panel shows the results for patients (x) and for their age-matched controls (○). (**A** and **B**) The results for the right and left eyes, respectively, of 12 patients treated for bilateral congenital cataract. (**C**) The results for the treated eyes of 16 patients treated for unilateral congenital cataract. The dashed lines represent the geometric mean acuity for patients. (**D**) The results for the fellow nondeprived eyes of the 16 patients treated for unilateral congenital cataract.

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about 1 octave at the 1-month test (*14*). The amount of improvement between the immediate and 1-hour tests and between the immediate and 1-month tests was not related to the age of first patterned visual input (P's $>$ 0.10, Pearson correlations) and did not differ for eyes that had been deprived unilaterally versus bilaterally (P's $>$ 0.10, two-tailed t tests) (Figs. 2 and 3). Nor, in unilateral cases, was the improvement over the month related to the amount of patching of the nondeprived eye ($P > 0.10$) (*15*). The improvement is unlikely to be merely a practice effect because there was no significant improvement over the first hour or the next month in the nondeprived eyes of unilateral patients, nor in any of the groups of age-matched controls (all P's > 0.10, one-tailed paired t tests comparing immediate to 1-hour and 1-month tests) (*16*).

The results indicate that in humans, acuity does not improve postnatally until the nervous system receives patterned visual input. For deprivation lasting up to 9 months after birth, acuity remains near the newborn level, perhaps maintained by cortical stimulation from spontaneous retinal activity (*17*). However, in this age period, patterned visual input can alter the nervous system rapidly and sufficiently to support better acuity as early as 1 hour later and to induce further improvement over the next month. These functional changes may reflect changes in cortical connectivity of the type that has been observed in kittens immediately after the onset of visual input (*18*).

The initial results after monocular deprivation were similar to those after binocular deprivation: In both cases the initial acuity was similar to that of normal newborns, and in both cases there was similar improvement after 1 hour of visual input. Although improvements after the 1-hour test occurred more rapidly after binocular deprivation (Fig. 3) (*14*), by the 1-month test eyes treated for monocular cataract had improved to the same extent as eyes treated for binocular cataract, whether or not there had been extensive patching of the nondeprived eye. This pattern contrasts with the results from later tests with similar cohorts, in which the acuity of the previously deprived eye in monocular cases is worse than the acuity in binocular cases, unless the fellow eye was patched aggressively after treatment for monocular cataract (*19*). The later results have been interpreted as showing that the nervous system is affected adversely both by deprivation and by unbalanced competition between a formerly deprived eye and a fellow nondeprived eye. Immediately after deprivation, as in kittens (*11*), recovery appears to be driven exclusively by visual activity. Only later, after visual activity has initiated the functional changes that we observed, do competitive interactions appear to affect the total amount of recovery.

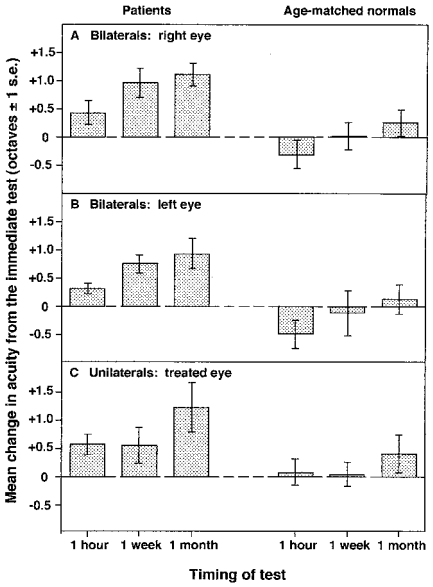

Fig. 3. Mean change (±1 SE) in acuity from the immediate test after 1 hour of visual input, 1 week later, and 1 month later. The *y* axis gives the amount of change in octaves, where one octave is a doubling or a halving of a value. Values above zero represent an improvement from the immediate test; values below zero represent a decline. Each panel shows the results for patients (left) and their age-matched controls (right). (**A** and **B**) The results for the right and left eyes, respectively, of the patients treated for bilateral congenital cataract. (**C**) The results for the deprived eyes of the patients treated for unilateral congenital cataract.

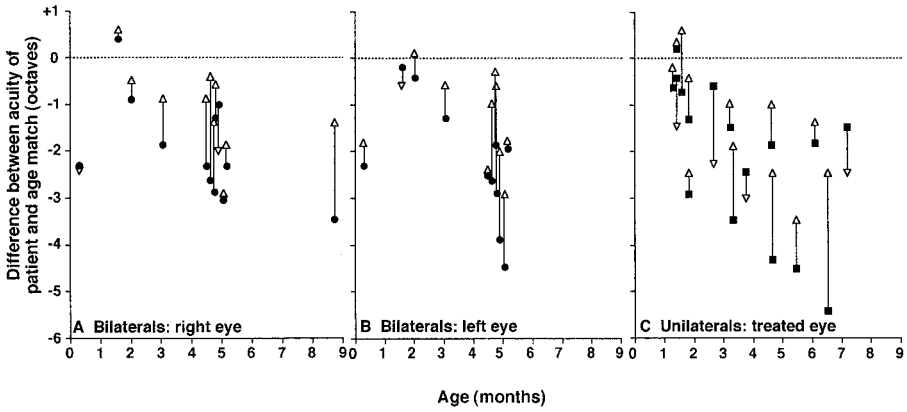

Fig. 2. Difference between each patient's acuity and that of the age-matched control at the immediate and 1-hour tests. The *x* axis indicates the patient's age at the time of the test, that is, at the time of the first patterned visual input. The *y* axis shows the patient's acuity relative to normal [$\log_2$ acuity of the control (in minutes of arc) minus $\log_2$ acuity of the patient] on the immediate test (filled symbols) and after 1 hour of visual input (open symbols). Differences are in octaves, where one octave is a doubling or a halving of a value. Negative values indicate that the patient's acuity was lower than normal. Upward-pointing arrows indicate an improvement relative to the age-matched control between the immediate and 1-hour tests; downward-pointing arrows indicate a decline. (**A** and **B**) The results for the right and left eyes, respectively, of the patients treated for bilateral congenital cataract. (**C**) The results for the deprived eyes of the patients treated for unilateral congenital cataract.

References and Notes

1. A. Brown and M. Yamamoto, *Am. J. Ophthalmol.* **102**, 245 (1986).
2. M. Courage and R. Adams, *Optom. Vision Sci.* **67**, 713 (1990).
3. V. Dobson, T. L. Schwartz, D. J. Sandstrom, L. Michel, *Dev. Med. Child Neurol.* **29**, 199 (1987).
4. D. L. Mayer and V. Dobson, *Vision Res.* **22**, 1141 (1982).
5. S. Miranda, *J. Exp. Child Psychol.* **10**, 189 (1970).
6. J. van Hof-van Duin and G. Mohn, *Vision Res.* **26**, 909 (1986).
7. Dense and central cataracts had been diagnosed on the first eye exam, which was always before 6 months of age. The cataracts were judged to block all patterned visual input to the retina because the infant did not fixate objects or follow moving stimuli; because the ophthalmologist could not visualize the fundus through the undilated pupil; because no red reflex was reflected through the undilated pupil; because the ophthalmologist noted the cataract to be dense and central; or for a combination of these reasons. Patients with one or more common associated conditions, namely misaligned eyes, nystagmus, or small cornea, were included in the sample. Those with other conditions likely to cause poor visual results (for example, prematurity, developmental delay, persistent hyperplastic primary vitreous, secondary glaucoma, or detached retina) were excluded.
8. Infants treated for bilateral cataracts always received the contact lenses for both eyes at the same time.
9. Informed consent was obtained after the nature and possible consequences of the studies were explained. Acuity was measured monocularly with Teller Acuity Cards [D. Y. Teller, M. A. McDonald, K. Preston, S. L. Sebris, V. Dobson, *Dev. Med. Child Neurol.* **28**, 779 (1986)] combined with the Dobson procedure to minimize the effect of observer bias [T. L. Lewis, M. J. Reed, D. Maurer, P. A. Wyngaarden, H. P. Brent, *Clin. Vision Sci.* **8**, 591 (1993); C. Mash, V. Dobson, N. Carpenter, *Vision Res.* **35**, 303 (1995)]. The tester was given a subset of cards with stripes of decreasing size and determined the smallest stripes for which the baby showed a consistent preference. The tester was masked to which of nine possible subsets was used for each test and whether the stripes were to the right or left on each card. The treated eyes were tested while patients were wearing a contact lens that focused stimuli at the testing distance. The two eyes of each patient were tested in random order on the immediate test and in alternating order on subsequent tests. Test order was the same for the matching normal infant, who was within 3 days of

the patient's age at each testing point. Patients (and their age-matched controls) were included only if they completed both the immediate and 1-hour tests for both eyes. For the comparison to the patient's immediate and 1-hour tests, the control infant was tested upon arrival at the lab and again after 1 hour of additional visual experience. Later measurements were available for most patients (and their controls) and occurred 1 week (mean, 1 week; range, 1 to 2 weeks) and 1 month (mean, 5 weeks; range, 3 to 8 weeks) after the immediate test.

10. C. J. Beaver, D. E. Mitchell, H. A. Robertson, *J. Comp. Neurol.* **333**, 469 (1993); D. E. Mitchell, G. Bateman, C. J. Beaver, P. Ritchie, *Invest. Ophthalmol. Visual Sci.* **35**, 1773 (1994); K. M. Rosen, M. A. McCormack, L. Villa-Komaroff, G. D. Mower, *Proc. Natl. Acad. Sci. U.S.A.* **89**, 5437 (1992); G. Mower, *Mol. Brain Res.* **21**, 47 (1994).
11. D. Mitchell and G. Gingras, *Curr. Biol.* **8**, 1179, R897 (1998).
12. Tables containing the acuity measurements at each test point for patients and their age-matched controls are available at www.sciencemag.org/feature/data/1037371.shl.
13. D. L. Mayer *et al.*, *Invest. Ophthalmol. Visual Sci.* **36**, 671 (1995).
14. Although both bilateral and unilateral cases improved significantly between the 1-hour and 1-month tests (all P's < 0.02), bilateral cases showed an improvement in each eye between 1 hour and 1 week (both P's < 0.05) but unilateral cases did not ($P > 0.10$) (Fig. 3).
15. Across patients, the mean number of hours per day that the nondeprived eye was patched during the first month ranged from 0 to 7.7 hours/day with an overall group mean of 4.6 hours/day.
16. The fact that the nondeprived eye of children treated for unilateral congenital cataract improved on average 0.26 octaves between the immediate and 1-hour tests raises the possibility that some of the improvement in the treated eyes might have arisen from nonvisual factors such as recovery from the eye exam. However, the improvement in the nondeprived eyes was not significant ($P > 0.20$, two-tailed t test), and the treated eyes of unilateral cases tended to improve more than the fellow nondeprived eyes, on average 0.32 octaves more ($P = 0.07$, one-tailed paired t test). There was no such improvement in 17 additional infants in a control experiment in whom one treated eye (eight from bilateral cases and nine from unilateral cases) was patched between the two tests instead of receiving 1 hour of patterned visual input, with a mean decline of 0.19 octaves. Between the immediate and 1-hour tests, acuity improved more in eyes from the main experiment that had received visual input during the hour than in eyes from the control experiment that had not and this was true whether the initial deprivation had been binocular or monocular (all P's ≤ 0.02, one-tailed unpaired t tests). In the six bilateral cases included in the control experiment for which we were able to measure changes in acuity both for the eye that had been patched and for the fellow eye that had received 1 hour of visual input, the experienced eye improved by a mean of 0.50 octaves, whereas the patched eyes declined by a mean of 0.24 octaves ($P = 0.04$, one-tailed paired t test). Although the significant difference results from both a significant decline in patched eyes and a nonsignificant increase in experienced eyes, it nevertheless indicates that the nervous system is sensitive to short-term changes in visual input and that recovery from the eye exam and contact lens insertion (which should have been equal in patched and experienced eyes) does not account for any improvement in acuity. The mean increase of 0.50 octaves in the experienced eyes is similar in magnitude to the mean from the main experiment (Fig. 3) and almost significant despite the small n (paired t test comparing immediate and 1-hour acuity for six experienced eyes, $P = 0.08$, one-tailed). The robustness of the improvement observed at 1 hour in the experienced eyes in the main and control experiments was confirmed by the finding that their acuity remained significantly better than the initial value when they were retested at 1 week, whereas there was no change in the nondeprived eyes in unilateral cases nor in the age-matched groups (unilateral cases in the main experiment: $P < 0.05$; right eye of bilateral cases in the main experiment: $P < 0.002$; left eye of bilateral cases in the main experiment: $P < 0.0001$; six experienced eyes of bilateral cases in the control experiment: $P < 0.002$; nondeprived eyes of unilateral cases in the main and control experiments, both P's > 0.10; age-matched groups, all P's > 0.10). The pattern of improvement after the onset of patterned visual input was also confirmed in eyes from the control experiment that were patched during the first hour after treatment; they improved significantly between the immediate and 1-week tests, with average improvements similar to those shown in Fig. 3 for the main experiment: 0.58 octaves in unilateral cases ($n = 9$; $P = 0.03$, one-tailed paired t test) and 0.88 to 1.24 octaves in bilateral cases (nine right eyes, $P < 0.004$; seven left eyes, $P < 0.02$).
17. C. J. Shatz, *Proc. Natl. Acad. Sci. U.S.A.* **93**, 602 (1996).
18. A. Antonini and M. P. Stryker, *Science* **260**, 1819 (1993).
19. T. L. Lewis, D. Maurer, H. P. Brent, *Invest. Ophthalmol. Visual Sci.* **36**, 2081 (1995).
20. We thank K. Harrison and Bausch and Lomb (Toronto, Canada) for donating the contact lenses necessary for the tests of some patients; R. Barclay for clinical assistance; M. Tighe, C. Colle, and S. Geldart for technical assistance; E. Perruzza for scheduling the patients; the families of the infants who participated; and K. Murphy for comments. Supported by the Medical Research Council of Canada and by the National Institutes of Health (U.S.).

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Precisely Localized LTD in the Neocortex Revealed by Infrared-Guided Laser Stimulation

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In a direct approach to elucidate the origin of long-term depression (LTD), glutamate was applied onto dendrites of neurons in rat neocortical slices. An infrared-guided laser stimulation was used to release glutamate from caged glutamate in the focal spot of an ultraviolet laser. A burst of light flashes caused an LTD-like depression of glutamate receptor responses, which was highly confined to the region of "tetanic" stimulation (<10 micrometers). A similar depression of glutamate receptor responses was observed during LTD of synaptic transmission. A spatially highly specific postsynaptic mechanism can account for the LTD induced by glutamate release.

The locus of long-term potentiation (LTP) and LTD is still a matter of debate. Mainly indirect methods have been used to separate contributions of pre- and postsynaptic factors. As these analyses are based on assumptions concerning neurotransmitter release, the results have been controversial (*1*). More direct approaches, probing glutamate sensitivity during LTP by microiontophoresis, also yielded conflicting results (*2*). Therefore, techniques for applying exogenous receptor agonists over a time course and volume, which approximate the release of transmitter at a single synapse, are required (*3*). Such brief and localized releases of neurotransmitter can be achieved by focusing ultraviolet (UV) light on the slice to release glutamate from its caged form, which has been added to the slice superfusate. LTD can be induced in hippocampal neurons by direct glutamate application (*4*). We used the method of glutamate application by photolysis in combination with infrared videomicroscopy to address these questions.

The soma and dendrites of pyramidal neurons of layer V were visualized in neocortical slices with infrared videomicroscopy, with the use of a gradient contrast system (*5*). Neurons ($n = 55$) were recorded with patch-clamp pipettes in whole-cell mode (*6*). Caged glutamate was added to the superfusion medium, and presynaptic input was eliminated by the addition of tetrodotoxin (TTX) (1 μM) in all experiments without synaptic stimulation. With a setup developed especially for infrared-guided laser stimulation [Fig. 1A and supplementary figure (*7*)], we were able to direct a 1-μm UV spot under visual control on the surface of the neuron being studied. The UV spot was positioned on the dendrite at distances of 100 to 150 μm from the soma.

As glutamate is released from its caged form by constant UV flashes in constant quantities (*8*) and presynaptic input was blocked by TTX, any changes in neuronal responses had to be of postsynaptic origin. After establishing a baseline of responses by releasing glutamate every 20 s for 10 min, a train of 5-Hz light flashes for 1 min was used

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