Visual recovery after monocular deprivation is driven by absolute, rather than relative, visually evoked activity levels

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It is now well established that the anatomical and functional development of the central visual pathways of a number of higher mammalian species is activity-dependent [1–3]. This dependence was revealed by the functional effects of an early period of monocular deprivation, where one eye of a young animal was deprived for a time of patterned visual input. Subsequently, most cells in the visual cortex (area 17) could be excited only by visual stimuli delivered to the non deprived eye [4–6] and the animal appeared blind through the deprived eye [7,8]. These effects have been attributed to a competitive activity-dependent mechanism in development, whereby the two eyes compete for control of cortical cells [9,10]. There are, however, suggestions that the substantial recovery that can occur after monocular deprivation may be mediated by a different mechanism. Here, insight into the nature of this mechanism has been provided by monitoring the speed of changes in the vision of the deprived eye of a kitten after 6 days of monocular deprivation. Although both eyes were open during the recovery period, the kitten was able to see with its deprived eye only 2 hours after visual input was restored to this eye. The visual acuity of this eye improved rapidly in the first 24 hours and continued in an orderly way for 6 weeks. In contrast to the effects during monocular deprivation, which depend upon a competitive activity-dependent process, we propose that the events that follow deprivation rely on a mechanism driven by the absolute level of visually evoked activity through the formerly deprived eye.

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Results and discussion

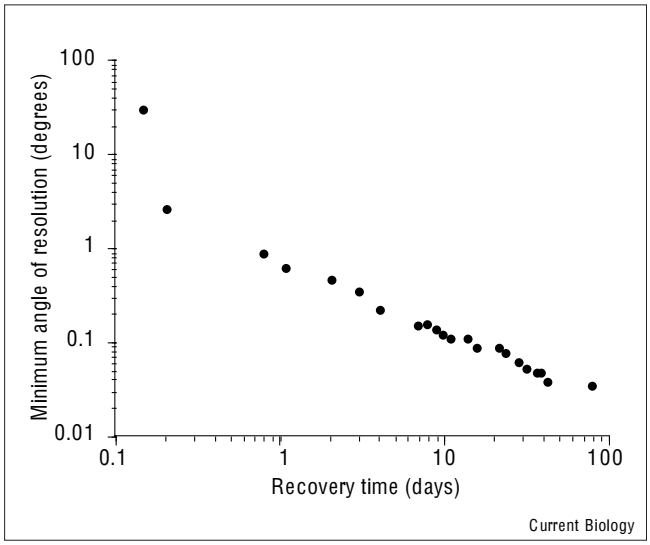
The data presented here were obtained using a kitten (C791) derived from an outbred domestic cat lineage that was raised from birth in a closed laboratory colony. At 35 days of age, the kitten's left eye was deprived of patterned visual input by eyelid suture under gaseous halothane anaesthesia, using surgical procedures that have been described in detail previously [11–13]. After 6 days, the eyelids of the closed eye were opened, and behavioural tests of the vision of the formerly deprived eye were begun 2 hours later by use of a jumping stand and procedures described in detail elsewhere [11–14]. The only departure from the customary test procedure was to employ a discrimination task rather than the usual detection task: the kitten, in a similar two-alternative forced choice task, was rewarded for choosing a vertical square-wave grating as opposed to an adjacent horizontal grating of the same spatial frequency and mean luminance. To permit such tests, an opaque contact lens occluder that had a curvature matched to that of the corneas of 6-week-old kittens [15] was placed over the nondeprived eye, after a drop of an ophthalmic local anaesthetic (Alcaine, from Alcon, Canada, at 0.5%) had been placed into the conjunctival sac of the occluded eye to alleviate any potential discomfort. The procedures were in accordance with the standards and regulations established by the Canadian Council on Animal Care.

Rapid changes in the vision of the deprived eye were evident within a few hours of restoration of visual input to this eye, even though no manipulations of the other eye were made at the same time to reduce its competitive advantage. Two hours after visual input had been restored to the deprived eye the animal appeared completely blind in this eye. Operationally, this meant that, when using its formerly deprived eye, the kitten appeared unable to distinguish a closed from an open door on the jumping stand from only 2 cm without recourse to tactile cues. Only a little over an hour later, however (3.25 hours after the eye was opened), the kitten was able to pass this test with ease. Moreover, the animal demonstrated clear signs of the presence of form vision, as it could jump correctly to a grating as opposed to an adjacent uniform field of the same mean luminance. More importantly, the animal was able, using the formerly deprived eye, to discriminate correctly the orientation of gratings having a period of as low as 25.6 mm from a distance of 26 cm (a spatial frequency of 0.18 cycles/degree). In three subsequent testing sessions conducted over the next 21 hours, the acuity of the deprived eye improved steadily to 1.25 cycles/degree. Thereafter, tests of the vision of the deprived eye were made at 1–6 day intervals, alternating with measurements of binocular visual acuity in order to monitor the slower improvement with age of the visual acuity of the nondeprived eye. The visual acuity of the deprived eye stabilized

after about 6 weeks at a little over 5 cycles/degree, at which time the other eye had attained an acuity of 7.05 cycles/degree, a value within the normal range reported in earlier studies [8,12,13] that used similar behavioural testing procedures.

In addition to the initial speed of visual recovery of the formerly deprived eye that was particularly evident in the first 24 hours, another prominent feature was the orderly nature of this recovery. The latter point was made most evident when the data were plotted on logarithmic scales, in order to make the early stages of recovery more evident. We also found it convenient to express the vision of the deprived eye in terms of the reciprocal of the visual acuity: namely, the angular size of the smallest grating period that could be resolved at the time of measurement. This value has been referred to in the past [16] as the minimum angle of resolution (MAR). Conceptually, it may be related to the dimensions of aggregated receptive fields of lower order cells innervated by the deprived eye that have established active connections with cells in the visual cortex at any point in time. When both MAR and recovery time are plotted on logarithmic scales, as displayed in Figure 1, the improvement in the MAR with time appears approximately linear, a finding which suggests that the two variables are related to each other by a power function. The very first measurements of MAR may underestimate the true extent of visual recovery because the rudimentary vision recovered at this point may have been insufficient to guide the motor behaviour required on the jumping stand.

Figure 1

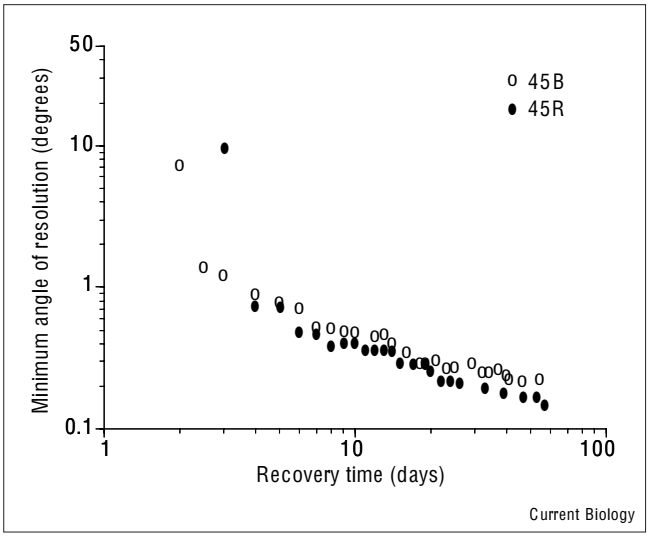


Very fast recovery of vision in the deprived eye of a kitten following a 6 day period of monocular deprivation imposed at 5 weeks of age. Formal tests of visual acuity were made using a jumping stand and procedures that have been described in detail elsewhere [11–14]. Training was begun when kitten C791 was 23 days old. At 35 days of age, just prior to the period of monocular deprivation, the visual acuity of each eye was 2.6 cycles/degree. Tests of visual acuity of the nondeprived eye were made daily during the 6 days of monocular deprivation, and at its termination the acuity of this eye was 2.9 cycles/degree. Measurements of the vision of the deprived eye were made every few hours for the first day but thereafter only daily and progressively less frequently as the rate of change of vision slowed.

The most striking feature of the results was the speed with which the vision of the deprived eye began to improve once visual input had been restored to it. Although the animal appeared blind with the deprived eye when tested at 2 hours, signs of form vision were quite evident only a little over an hour thereafter. This rapid recovery was all the more remarkable in view of the fact that the other eye remained open during the recovery period and no manipulation was made to reduce its overall competitive advantage, in terms of the strength of the neural connections it had established with the visual cortex during the period of closure of the deprived eye. Moreover, although the 6 day period of deprivation could be considered short in absolute terms, it has nevertheless been shown to be of sufficient duration to produce as great a shift of ocular dominance among cortical cells in area 17 as that induced by months of deprivation [5,6]. At an anatomical level, the extent to which geniculocortical axon arbours are resculptured following monocular deprivation have been reported to be no greater after 4 weeks of deprivation than after 6 days [17]. Even though the immediate anatomical and physiological effects of the 6 days of deprivation were likely to have been very substantial, the subsequent behavioural recovery was rapid and was mediated by a non-competitive process.

The idea that the recovery that follows monocular deprivation involves a non-competitive process was strengthened further by re-examination of earlier data [7,8] from experiments in which direct comparisons had been made between the changes in the vision of the formerly deprived eye in two recovery conditions. One of these conditions, in which both eyes were open during recovery, was the same as that experienced by C791, and was referred to as binocular recovery. In the second condition, the eyelids of the other eye were closed during recovery so that the animal was forced to employ its deprived eye, a situation referred to as reverse suture [18]. Figure 2 displays the earlier data [7,8] from two littermates, 45B and 45R, replotted in the same form as the data shown in Figure 1. The recovery of vision in both animals conformed to a similar power function to that shown by C791 and during the first 3 weeks was closely comparable in the two recovery conditions. The final extent of visual recovery was somewhat greater in the animal that was reverse lid-sutured (45R), a finding that was even more evident in the extent of the physiological recovery [7]. A similar parallel speed of visual recovery was observed earlier [7,8] in

Figure 2



The recovery of vision in the deprived eye following monocular deprivation proceeds at the same speed in two conditions of recovery. In one condition (animal 45B), both eyes were open following monocular lid-suture from near birth to 45 days of age, while in the other (45R), the formerly nondeprived eye was sutured closed so as to force the animal to use its formerly deprived eye. The ordinate shows the visual acuity for square-wave gratings as measured on a jumping stand and replotted from earlier reports [7,8] onto logarithmic scales as in Figure 1.

littermates deprived up to 60 days of age, and this has been reinforced by later observations from many other animals [8,13]. The close similarity of the tempo of the changes in vision of 45B and 45R (Figure 2) over the first 3 weeks suggests that the initial recovery following reverse lid-suture may be mediated by the same process as underlies that observed in binocular recovery. Indeed, on the basis of the behavioural findings from 45R, it could be proposed that a competitive process may have interceded following reverse lid-suture in only the latter stages of recovery and that its benefits became apparent only after the formerly deprived eye had been able to mediate form vision for about 3 weeks.

On the basis of these various observations, we propose that the effects of monocular deprivation and the recovery that occurs afterwards involve different processes. Whereas the functional and anatomical effects of an early period of monocular deprivation can be explained best in terms of the operation of a competitive activity-dependent process, we suggest that the visual recovery following termination of monocular deprivation relies on the absolute level of visually evoked activity mediated by the formerly deprived eye. Furthermore, we suggest that the same activity-dependent process mediates the initial stages of visual recovery following reverse lid-suture. According to this scenario, a competitive mechanism operates only after a scaffold of connections with the formerly deprived eye has been established in area 17 by a mechanism that is responsive to the absolute level of visually evoked neural activity in geniculocortical afferents from that eye. The idea that recovery from monocular deprivation may involve different processes from those responsible for the effects of that deprivation is supported by the recent finding [19] that certain protease inhibitors can block the anatomical and physiological effects of reverse occlusion but not the effects of monocular deprivation; this result suggests that there may be only partial overlap between the cascade of molecular events that are initiated during monocular deprivation and those that follow its termination.

A number of recent observations point to possible substrates underlying the speed with which the first signs of vision become evident in the formerly deprived eye. Most significantly, changes in gene expression have been reported in visual cortex following brief alterations of visual input [20–23]. In dark-reared kittens, substantial changes in expression of a number of immediate early genes have been reported following one hour of visual exposure [20,21]. Moreover, the protein products of certain of these genes are detectable after just 30 minutes exposure to light [21,24]. Such rapid changes in expression of these, and of other as-yet unidentified genes, may form part of the initial cascade of events that mediate the known anatomical and functional changes that occur within hours of deprivation or its termination. Nevertheless, the well-known finding that functional recovery is both slower and less profound with increase in the length of deprivation and/or the age at which it is terminated [1,3] implies that equivalent amounts of visually evoked afferent activity produce different effects as the animal ages, because of a decline in the extent of residual plasticity in the visual cortex.

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