Visual effects of damage to P ganglion cells in macaques

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Abstract

Four indices of visual performance were measured in control macaques and in macaques that had been exposed to monomeric acrylamide, a neurotoxicant that preferentially damages P retinal ganglion cells. Morphological examination of the retina and visual pathways of these monkeys showed virtually complete loss of P ganglion cells over a region extending to at least 40 deg from the fovea, and relative sparing of M ganglion cells. The four tests examined visual functions for which the visual pathway from P ganglion cells might be of great importance: visual acuity, contrast discrimination, hyperacuity, and shape discrimination.

In the acrylamide-dosed monkeys, visual acuity was reduced slightly more than fourfold, a somewhat larger reduction than that seen previously after ibotenic-acid lesions of the P pathway in the geniculate. The residual acuity was in good agreement with the Nyquist frequency calculated from the density of ON or OFF M ganglion cells. Contrast increment thresholds were elevated for the control monkeys only in one of the two conditions tested. The elevation was found only under those spatiotemporal conditions for which we have previously shown that contrast thresholds are increased by acrylamide exposure, and was most marked at low background contrasts.

Vernier acuity was elevated in one control monkey, but not affected in a second monkey that also had severe loss of P ganglion cells. Finally, we found no effect of acrylamide exposure on the number of training trials required to learn simple or complex shape discriminations. These results support previous findings in showing that the P pathway mediates visual acuity, and they show that several other important aspects of visual perception are not exclusively dependent on the P pathway.

Keywords: Parallel pathways, Sampling density, Macaque monkey acuity, Shape discrimination

Introduction

The P pathway is one of the two major retinocortical visual pathways in macaque monkeys and humans (Leventhal et al., 1981; Perry et al., 1984). It consists of approximately 80% of the retinal ganglion cells, and this proportion is rather constant across the retina (Lynch et al., in preparation). The P pathway originates in ganglion cells that are of moderate soma size, have small dendritic fields, show color-opponent physiological responses, and project to parvocellular layers of the lateral geniculate nucleus (deMonasterio & Gouras, 1975; Leventhal et al., 1981; Perry et al., 1984), hence the term P cells. In recent years, much attention has been devoted to determining the role of the P pathway, and contrasting it to that of the less-prominent M pathway that projects to magnocellular layers of the lateral geniculate nucleus (LGN). Studies to date have used acrylamide-induced damage to P retinal ganglion cells (Merigan, 1989; Merigan & Eskin, 1986), or ibotenic-acid lesions of parvocellular layers of the geniculate (Merigan et al., 1991; Schiller et al., 1990a) to show that the P pathway mediates color vision, visual acuity, and contrast sensitivity at high spatial and low temporal frequencies. Similar studies, using ibotenic-acid lesions of magnocellular layers of geniculate, demonstrated that the M pathway is primarily involved in the detection of low spatial and higher temporal frequencies (Merigan & Maunsell, 1990; Schiller et al., 1990a). A subsequent study examined the possibility that the M pathway might mediate motion perception, but found that neither direction nor velocity discriminations were seriously affected by M pathway lesions (Merigan et al., 1991b).

The present study examined the effect of acrylamide-induced damage to retinal ganglion cells of the P pathway on four visual capacities: acuity, contrast discrimination, vernier acuity, and shape discrimination. The acuity measurement extended a previous study that showed that ibotenic-acid lesions of the P pathway in the lateral geniculate caused a 3-4-fold reduction in visual acuity (Merigan et al., 1991b). Contrast discrimination was examined because physiological studies have shown that the contrast gain of M cells in the lateral geniculate is high and saturates at relatively low contrasts, while that of P cells is low and linear (Shapley et al., 1981), suggesting that the P pathway may be essential to contrast discrimination at high base contrasts. Vernier acuity was tested because spatial resolution and contrast

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sensitivity at low temporal frequencies depend on the P pathway (Merigan et al., 1989; Merigan & Eskin, 1986), and it could be argued from this that the P pathway should play a prominent role in vernier resolution for stationary targets. Finally, shape discrimination was studied because the P pathway provides the major input to cortical areas V4 and the inferotemporal cortex (IT) (Maunsell & Newsome, 1987), which have been implicated in form perception (Gross, 1972).

Methods

Subjects and dosing

The subjects were eight feral, adult (approximately 5-kg body weight), female monkeys (Macaca nemestrina), none of which had more than 0.5D of refractive error in either eye. They had free access to monkey chow, supplemented regularly with fresh fruit, and their water was withheld for approximately 20 h before threshold testing 5 days each week. Five of the monkeys served as normal controls, while the other three (561, 117, and 310) were orally dosed 5 days per week with 10 mg/kg of acrylamide monomer (Eastman Kodak Co., Rochester, NY) in fruit juice. Monkey 310 received 50 doses during one dosing period, while monkeys 117 and 561 underwent two periods of dosing (with 39 and 50 doses during each period, respectively) separated by a 5- or 23-month recovery period. The health of each monkey was closely monitored during the period of dosing (Merigan, 1989). Visual thresholds for luminance and chromatic contrast sensitivity of monkeys 117 and 310 have previously been published (Merigan, 1989; Merigan & Eskin, 1986).

Visual testing

The monkey was seated in an acrylic chair facing a display device on which the test stimuli were presented. All measures, except visual acuity, were obtained binocularly with free viewing of the stimuli. This technique makes it possible for subjects to use whichever portion of the visual field is most sensitive for the task at hand. Nonetheless, we are quite confident that the discriminations described in this paper were performed with the central portion of the visual field, the region that was devoid of P cells. Our basis for this conclusion is described for each of the tasks in the Discussion. Test sessions consisted of a series of trials, with the start of each trial marked by the onset of a tone, and each trial lasting until a choice was made. All four experiments involved a two-alternative forced choice, in which the two stimuli were presented in a random sequence, and the monkey chose by pressing the right or left push button on the response panel. Correct choices were rewarded with a brief delivery of fruit juice through a stainless-steel spout, while incorrect choices were followed by a 6-s beeping tone. A 4-s intertrial interval then followed. A correction procedure was in effect throughout all testing to prevent the development of position biases. If the monkey made three consecutive errors during presentation of one of the two stimuli, only that stimulus was presented on subsequent trials until the monkey made a correct response. Such correction trials were excluded from data analysis, and following a correct response, the sequence of stimuli was again random. In the acuity experiment, the monkey reported whether the stimulus was horizontal or vertical, while in the other experiments the monkey chose one of two stimuli presented side by side. A summary of the stimuli and testing procedures for the four experiments appears in Table 1, and further details follow. Thresholds were measured in the acuity, contrast discrimination, and vernier acuity experiments using a staircase procedure in which the discrimination became one step more difficult (with probability 0.33) after each correct response, and became easier by one step after each error. Thresholds were calculated from the daily psychometric function by interpolation to 75% correct responding. Performance in the form-discrimination experiment was determined from the number of trials required to reach criterion performance level (at least 90% correct in a block of ten trials). All daily testing sessions consisted of 200 trials, except for the 100-trial form-discrimination sessions.

Visual acuity

Acuity was tested with vertical or horizontal sinusoidal grating stimuli of 0.55 Michelson contrast \( \frac{(L_{\text{max}} - L_{\text{min}})}{(L_{\text{max}} + L_{\text{min}})} \), presented on a high-resolution display oscilloscope (Tektronix 606 with P-31 phosphor). The monkey reported on each trial whether the grating was vertical or horizontal, and the limit of spatial resolution was measured by varying the spatial frequency of the grating. After initial training on this task, the monkey was anesthetized with isoflurane and a scleral search coil implanted in its right eye (so that eye position could be monitored) and a stainless-steel sleeve attached to its skull (so that the head could be immobilized) (Judge et al., 1980). Acuity was tested monocularly along the horizontal meridian of the right eye at a range of eccentricities, with the retinal locus of the

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<td>Measure As a function of Psychophysical task Stimulus display</td>
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<td>Acuity threshold Eccentricity Orientation discrimination Tektronix 606 high-resolution oscilloscope</td>
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<td>Contrast increment Background contrast Spatial forced-choice Hewlett Packard 1332 oscilloscope</td>
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<td>Vernier acuity Dot separation Spatial forced-choice 2 Tektronix 606 high-resolution oscilloscopes</td>
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<td>Form discrimination Trials to criterion Seven stimulus pairs Spatial forced-choice Conrac 7211 color monitor</td>
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stimulus varied by controlling fixation. In this procedure, onset of the trial and presentation of the stimulus required both completion of the intertrial interval and fixation of the monkey within a ±0.33 deg window around the HeNe laser fixation spot. The diameter of the test grating was varied by changing the aperture in the unilluminated white surround through which the stimulus was viewed. Locations tested for the acrylamide-dosed monkey (561) were 0, 3, 6, 9, and 12 deg along both nasal and temporal field horizontal meridia, and 25 deg in the temporal field. Target sizes were 1.0 deg at 0-deg, 2.0 deg at 3- and 6-deg, and 3.0 deg at 9-, 12-, and 25-deg eccentricity. The test target was 185 cm from the monkey's eye for eccentricities of 0, 3, and 6 deg, and 93 cm for greater eccentricities. Conditions for the control monkeys, which had considerably higher acuities, differed only in the use of smaller test targets (0.5, 1, 1.5, 3, 3, and 3 deg for eccentricities of 0, 3, 6, 12, 20, 25, and 30 deg, respectively), and are described in detail in Merigan and Katz (1990).

Contrast discrimination
Two patches of gratings of identical mean luminance, spatial frequency, and temporal frequency were displayed on an HP1332 oscilloscope at a distance of 100 cm and viewed through two 5-cm-diameter circular apertures (separated by 1.5 cm) in an unilluminated white surround. At the beginning of each trial, the contrast of the two stimuli was identical, and then the contrast of one was smoothly increased (following a raised cosine waveform of temporal frequency 0.5 Hz) to the test value. The monkey's task was to choose the stimulus of higher contrast. Within each daily session, the spatial and temporal frequency of the gratings were fixed, but between daily sessions a wide range of spatial frequencies and frequencies of temporal counterphase modulation was tested.

Vernier acuity
The monkey faced two high-resolution display oscilloscopes (Tektronix 606, Tektronix, Beaverton, OR), at a distance of 114 cm, that were separated, center to center, by 66 cm. The testing room was dark and the faces of the displays were unilluminated except for two spots near the center of each that were vertically separated by 4, 16, or 64 min arc in the three test conditions. Each spot was set to 2 log units above detection threshold for a human observer. On each trial, the bottom spot on one of the two displays was displaced either to the right or left of vertical alignment with the spot above it. The monkey was required to choose the side on which the spots were misaligned.

Form discrimination
The monkey faced a 19-inch color monitor (Conrac 7211, Conrac, Covina, CA), which displayed a uniform white between trials, at a distance of 150 cm. After a 4-s intertrial interval, two different achromatic form stimuli were presented on the display, with the right/left position randomized. Both the time of appearance of the stimuli and the opportunity to respond were marked by the onset of a tone. The seven pairs of stimuli that were used for this experiment are shown in order of presentation from top to bottom in Fig. 1 in their correct orientation and relative size. Stimulus pairs 1 and 2 have been used in studies of inferotemporal cortex lesions (Gross, 1972). Stimulus pair 3 cannot be resolved using peripheral vision. Stimulus pairs 4–7 require the use of very different types of features for discrimination. The greatest horizontal extent of the stimuli in units of visual angle was as follows: stimuli 1, 4, and 5 were 5.6 deg; stimulus 2 was 4.4 deg; stimulus 3 was 0.9 deg; stimulus 6 was 4.6 deg; and stimulus 7 was 5.2 deg. In stimulus pair 7, the position of dots in the right stimulus were randomly jittered ±15% of the interdot spacing. The stimulus shown here on the right of each pair was designated as correct, and choices of that stimulus were rewarded as described above. Each pair of stimuli was presented throughout full sessions of 100 trials until criterion performance of at least 90% correct performance in a block of ten trials was achieved by both monkeys.

Histology
Monkeys 561 and 310 were sacrificed about 8 and 50 months, respectively, after the end of the last dosing period. Monkey 117 died unexpectedly about 48 months after the last dosing period and could not be perfused, so its brain was immersion fixed in 1% paraformaldehyde/1.25% glutaraldehyde in phosphate-buffered saline (PBS). At sacrifice, monkeys 561 and 310 and several control monkeys were deeply anesthetized with 15 mg/kg of ketamine (i.m.), followed by 25 mg/kg i.v. pentobarbital. After an i.v. injection of 2500 or 5000 units of heparin, the chest was opened and tissues fixed by sequential transcardial perfusion with (1) PBS, (2) 1% paraformaldehyde/1.25% glu-
taraldehyde in PBS, and (3) 5% glycerol in PBS. Brains were removed and blocked, and 40-μm-thick frontal sections were cut, providing alternating sections for cytochrome-oxidase histochemistry (Wong-Riley, 1979), and Nissl staining with cresyl violet.

**Ganglion cell counts**

Eyes from monkeys 561 and 117 were removed prior to perfusion with fixative, and the retinas, as wholemounts, were stained by the Gross-Schultze reduced silver nitrate method (Silveira & Perry, 1990). M ganglion cell density was estimated from these retinas using procedures that have been previously described (Silveira & Perry, 1991). Control data from these M cell counts were taken from a previous study of retinas of three *Macaca fascicularis* and three *Macaca mulatta* monkeys (Silveira & Perry, 1991).

Estimates of non-M ganglion cell density (which should include P ganglion cells and ganglion cells projecting to the midbrain) were calculated by subtracting M ganglion cell density from total ganglion cell density. The latter measure was determined by counting all neurofibrillar-positive neurons (M cells) plus other lightly stained non-M cells. Non-ganglion cells most likely did not contaminate these counts, because staining was frequently clear enough to classify the cells by their dendritic and axonal morphology, and the technique does not regularly stain primate amacrine cells (Silveira & Perry, 1991). Control data for total ganglion cell counts were taken from four retinas of *Macaca mulatta* (Perry et al., 1984).

All counts were made from foveal to peripheral retina along the horizontal meridian in both nasal and temporal directions, and along the vertical meridian in dorsal and ventral directions. A retinal magnification factor of 0.223 mm/deg (Perry & Cowey, 1985) was used to convert retinal eccentricity from millimeter of retina to degrees of visual angle.

**Results**

**Histology**

The extent of acrylamide-induced loss of ganglion cells is illustrated in Figs. 2 and 3. Fig. 2 shows the residual density of non-M ganglion cells (which includes P ganglion cells and those ganglion cells that project to the midbrain) for two monkeys after acrylamide exposure, as well as for control monkeys. The left panel shows density along the horizontal meridian and the right panel along the vertical meridian. The dashed lines represent the mean data for two control monkeys. The dotted lines indicate the density consistent with survival of 10% of total ganglion cells (which is approximately the density of ganglion cells that project to the midbrain). Survival of non-M ganglion cells was about 10% in the nasal meridian and generally less than that in the other three meridia of the visual field. For technical reasons comparable data could not be obtained for the third acrylamide-exposed monkey (310). However, two measures that were obtained in this monkey suggested that ganglion cell loss was at least as severe as it was in the two monkeys illustrated in this figure. Counts of total neurons in the ganglion cell layer from Nissl stains showed a similar proportion of surviving neurons, and cytochrome-oxidase levels in the lateral geniculate (Lynch et al., in preparation) suggested loss of most P ganglion cells over the central 40 deg of the retina.

**Fig. 2.** Density of non-M retinal ganglion cells (i.e. total ganglion cells minus M cells) along the horizontal (left) and vertical (right) meridia of the right eyes of acrylamide-treated monkeys 561 (circles) and 117 (squares). The dashed line represents the mean for four control monkeys from Silveira and Perry (1991). The dotted line indicates the density consistent with sparing of 10% of total ganglion cells, i.e. the approximate density of ganglion cells projecting to the midbrain.

**Fig. 3.** Density of M retinal ganglion cells along the horizontal (left) and vertical (right) meridia of the central retina. Counts were obtained from Gross-Schultze-stained retinæ of acrylamide-exposed monkeys 561 (circles) and 117 (squares). Control data (stippled) represent the mean ± s.d. from six similarly stained macaque retinæ from Silveira and Perry (1991).

The survival of M retinal ganglion cells along the horizontal meridian is illustrated in Fig. 3 for two acrylamide-exposed monkeys (561: circles and 117: squares), and six control monkeys (Silveira & Perry, 1991). Again, the left panel shows the horizontal meridian and the right panel the vertical meridian. Neither acrylamide-exposed monkey showed a loss of retinal M ganglion cells compared to control monkeys in the nasal visual field. However, monkey 561 did show a moderate loss of M ganglion cells in the temporal field, although ganglion cell density could not be determined from 10- to more than 30-deg eccentricity for technical reasons. Along the ventral and dorsal meridia, M ganglion cells were spared in monkey 117 and slightly affected at some eccentricities in monkey 561.
Visual effects of P cell damage

Fig. 4. Visual acuity (cycles/deg) for the right eye of acrylamide-treated monkey 561 (triangles), and for the right eye of two control monkeys (Merigan & Katz, 1990) (circles and squares) along the horizontal meridian of the visual field. The dashed line shows the acuity predicted from the Nyquist frequency of sampling by P ON or OFF cells, and the dotted line a similar calculation for the M ganglion cells of the horizontal meridian of the right eye of monkey 561.

**Visual function**

In Fig. 4, the acuity of acrylamide-exposed monkey 561 along the horizontal meridian of the right eye is compared to that of two control monkeys (Merigan & Katz, 1990). Foveal acuity was reduced by almost a factor of 4, while eccentric acuity was decreased about 4–6-fold. As with ganglion cell density, acuity was more decreased in the temporal than the nasal field. The dashed curve shows the acuity predicted from the Nyquist frequency (Merigan & Katz, 1990) of ON or OFF P ganglion cells (Perry & Cowey, 1985), while the dotted curve shows that predicted from the Nyquist frequency of ON or OFF M ganglion cells of this monkey’s tested eye.

Fig. 5 illustrates threshold Weber ratios (increment contrast) as a function of background contrast for two control and two acrylamide-exposed monkeys for stationary gratings of 6 cycle/deg spatial frequency. The solid line indicates where contrast thresholds would fall if they were a constant Weber fraction (increment/background contrast) of 0.1. Contrast discrimination thresholds for the acrylamide-treated monkeys were elevated at all background contrasts, although the magnitude of the elevation was greatest at low background contrasts.

Fig. 6 also illustrates contrast-discrimination thresholds, although here the stimulus was a 0.7-cycle/deg grating modulated in counterphase at 10 Hz. Contrast difference thresholds under these conditions were similar in control and acrylamide-treated monkeys.

The control data in Fig. 7 (open symbols) show that vernier thresholds of control monkeys increased with dot separation, as has been reported previously for humans (Williams et al., 1984). Similar values for vernier acuity were obtained in acrylamide-treated monkey 310 (filled circles), while the other dosed monkey (117, filled squares) had elevated thresholds at all dot separations, but particularly at the 4-min separation.

We found no reliable difference in the number of trials required for an acrylamide-treated and a control monkey to reach criterion performance (at least 90% correct) on the seven dif-
different form-discrimination tasks illustrated in Fig. 1. The number of trials to criterion for acrylamide-treated monkey 310 were 30, 100, 30, 10, 10, 170, and 90, and for control monkey 410 were 30, 110, 80, 70, 160, 130, and 170 for the seven tasks. While there was wide variation from task to task in criterion performance, we found no evidence of a deficit in the performance of monkey 310 that might have been due to acrylamide exposure or the resulting P cell loss.

Discussion

The most dramatic visual deficit found in this study to be associated with loss of retinal P ganglion cells was the 4–6-fold decrease in visual acuity over a wide range of retinal loci. A loss of this magnitude is to be expected from the image sampling properties of retinal P and M cells, and a similar, albeit somewhat smaller, loss was measured after an ibotenic-acid lesion of the P pathway in the lateral geniculate nucleus (Merigan & Katz, 1990). The three other visual capacities that we measured appeared to be relatively insensitive to damage to the P pathway, indicating that they can be mediated reasonably well by other visual pathways. Contrast discrimination for 6 cycle/deg gratings was degraded in acrylamide-exposed compared to control monkeys, but this was likely due to the previously reported contrast sensitivity loss at 6 cycle/deg which reduces the visibility of both background and increment (Merigan & Eskin, 1986). No impairment was found for contrast discrimination measured with 0.7-cycle/deg stimuli modulated at 10 Hz, stimulus conditions for which there was no loss of contrast sensitivity in these monkeys (Merigan & Eskin, 1986). Vernier acuity was poorer in one acrylamide-exposed monkey, but a second exposed monkey with relatively complete loss of central P ganglion cells showed virtually the same vernier acuity as unexposed controls. This suggests, in agreement with previous theoretical work (Parker & Hawken, 1985), that vernier acuity may be mediated by the M pathway under some stimulus conditions. Finally, the one acrylamide-exposed monkey that we tested for the learning of simple form discriminations showed no obvious impairment relative to a control. Unlike the previous measures, this last study measured rate of learning rather than visual thresholds, and therefore may be especially dependent of the testing histories of the monkeys. However, it supports previous results (Merigan, 1991) in suggesting that many complex, visually mediated discriminations can be performed in the absence of either the P or the M visual pathway. The four experiments of this study strengthen the conclusion (Merigan, 1989; Merigan et al., 1991) that damage to the P pathway does not disrupt visual discriminations that are not completely dependent on visual characteristics uniquely transmitted by this pathway, such as fine details, color, or information about slowly moving or stationary stimuli.

Selective loss of P ganglion cells after acrylamide

In the macaque retina, approximately 80% of ganglion cells are P cells, 10% are M cells, and the remaining 10% consist of a mixture of cell types, most of which project to the midbrain (Perry & Cowey, 1984; Perry et al., 1984; Silveira & Perry, 1991). In the acrylamide-treated monkeys of this study, approximately 80% of retinal ganglion cells were lost over the central 40 deg of the retina compared to control monkeys. In contrast, M cells in central and nasal field appeared to be well preserved after acrylamide, although some loss was evident in the temporal visual field of monkey 561. Whether the remaining non-M ganglion cells were P cells, midbrain projecting cells, or a combination of the two could not be determined from our study, since both could contribute to the densities shown in Fig. 2. However, analysis of cytochrome-oxidase activity in parvocellular layers of the lateral geniculate nucleus in these monkeys suggests that very few P cells survived acrylamide dosing, perhaps less than 5% (Lynch et al., in preparation). Thus, most of the residual cells shown in Fig. 2 must belong to the 10% of ganglion cells that project to targets outside of parvocellular and magnocellular layers of the geniculate (Perry & Cowey, 1985), and these cells, as a group, must be little affected by acrylamide. Thus, the very substantial loss of ganglion cells over the central 40 deg of the retina in acrylamide poisoning is almost entirely confined to P cells, and there is virtually complete sparing of other classes of both larger and smaller ganglion cells.

Visual acuity

The visual acuity of monkey 561 was decreased about 4–6-fold across the visual field, relative to that of control monkeys. The substantial loss was not surprising, given that normal visual acuity appears to depend on the P pathway (Merigan & Katz, 1990; Merigan et al., 1991), and that the much lower sampling density of the M pathway should result in much lower acuity. In a previous study of visual detection by acrylamide-exposed monkeys (Merigan & Eskin, 1986), which included monkeys 117 and 310 of the present study, the visual acuity of the three dosed monkeys was little affected (20% to over a factor of 2 decrease). The smallest loss was found in monkey 117, and the anatomical results of this monkey, shown in Fig. 2 of this paper, seem inconsistent with such a small decrease. The likely explanation for this discrepancy is that, in the 1986 study, acuity was tested with a spatial forced choice between a high-contrast grating and no stimulus. Such a procedure may result in discrimination based on aliasing (Williams, 1985), i.e. the detection of patterns beyond resolution by the detection of aliased fringes. On the other hand, acuity was measured in the present study, and in the study of P pathway lesions (Merigan et al., 1991), by the discrimination of grating orientation, which makes it less likely that aliased fringes could mediate discrimination. This result emphasizes the importance of the choice of psychophysical procedure when testing spatial resolution.

That the residual acuity of monkey 561 was mediated by the M pathway is suggested by its close approximation to the prediction from the Nyquist sampling frequency of ON or OFF M cells in the retina of monkey 561 (dotted line in Fig. 4). It is unlikely that this acuity could be mediated by pathways other than the M pathway, such as those projecting to superior colliculus or pretectum, because the number of cells, and hence their sampling density, would be too low, and because some of the cells of this group have very large dendritic fields (Perry & Cowey, 1984), which would presumably reduce acuity by spatial averaging well below the level measured in monkey 561.

In calculating Nyquist-frequency predictions for the M pathway (shown by the dotted line in Fig. 4), we considered ON and OFF M cells to be separate populations, and thus, divided the M cell density by 2 before calculating the Nyquist frequency. We have previously used the same approach for calculating the Nyquist frequency of P ganglion cells (Merigan & Katz, 1990).
on the basis of the calculation (Schein & deMonasterio, 1987; Wäsßle et al., 1989) that there are more than two ganglion cells for each cone in the central retina of the primate, suggesting that ON and OFF ganglion cell matrices may receive independent input from each cone. This calculation is represented in Fig. 4 by the dashed line. It is not clear if the matrices of M ON and OFF ganglion cells might also function independently, although some support for this view is provided by the good agreement between the Nyquist frequency calculated for half of the M cell matrix and the acuity measured for monkey 561 in this study.

Use of the Nyquist calculation may only be appropriate if the cell density provides a reasonable estimate of the average intercell spacing, i.e. if the cells are regularly spaced. This reflects the possibility that it is really minimal or modal nearest-neighbor distance that determines the resolution capability of a matrix, and this can be estimated from density only if cells are regularly spaced. The best evidence for this possibility comes from an experiment by Williams and co-workers (Williams, 1990) who showed that the resolution of middle or long-wave-length sensitive cones in isolation was the same as that of both cone types together.

The results of this experiment indicate that the visibility of fine details is mediated entirely by the P pathway, but that in the absence of a P pathway, the M pathway can be used to resolve the orientation of gratings at about the Nyquist frequency for the M pathway. This result suggests some curious features of vision mediated by the M pathway. Physiological studies have shown that receptive-field centers of P and M cells, both in the retina and geniculate, are of similar size, and that individual neurons in the two pathways can resolve gratings of similar fineness (Crook et al., 1988; Derrington & Lennie, 1984). For P cells, the limit of resolution due to averaging across the receptive-field center is well matched to the resolution limit dictated by their sampling density (Merigan & Katz, 1990). This match insures that P cells do not transmit fringes (Williams, 1985) due to the aliasing of spatial frequencies above their resolution limit. M cells, on the other hand, have no such protection, and they should produce aliased fringes for all spatial frequencies between the resolution limit determined by their sampling density (which was measured in this study) and that much higher frequency limit set by spatial averaging over their receptive field. Thus, the M pathway should produce potentially bothersome aliased fringes whenever it views a stimulus that contains spatial frequencies above its resolution limit.

**Contrast discrimination**

It has been reported that the contrast gain (change in response per unit of contrast) of neurons in the P and M pathway are very different (Shapley et al., 1981), with that of M retinal cells and magnocellular LGN cells being high and beginning to saturate at contrasts as low as 30%, and that of retinal P cells and parvocellular LGN cells being low and not saturating at contrasts as high as 80% (Shapley et al., 1981). It has also been proposed that this difference may determine the role of these pathways in contrast discrimination (Shapley & Perry, 1986), with P cells probably dominating contrast discrimination at high base contrasts. On the other hand, a recent report (Sclar et al., 1999) suggested little difference in the contrast saturation of parvocellular and magnocellular neurons in the LGN. Lack of contrast saturation in even a small number of magnocellular neurons would argue against a specialized role for the M pathway in discriminating high contrasts.

The contrast-discrimination data of the present study indicates little effect of acrylamide exposure on this performance for a low spatial-frequency stimulus modulated at moderately high temporal frequency (Fig. 6). We have shown elsewhere (Merigan et al., 1991a) that visual sensitivity for such stimuli is dominated by the M pathway, and contrast sensitivity for this stimulus in monkeys 117 and 310 was comparable to that of controls (Merigan & Eskin, 1986). Thus, the data in this figure show no effect of removal of the P pathway on contrast discrimination for a condition in which threshold detection is dominated by the M pathway.

The data shown in Fig. 5 indicate a moderate disruption of contrast discrimination when detection of the stimulus is dominated by the P pathway (Merigan et al., 1991). In the acrylamide-dosed monkeys, contrast-discrimination thresholds are elevated at all base contrasts, and the elevation is greatest at low contrasts. The points on the far left of the graph represent contrast thresholds, and as was shown with a different technique (Merigan & Eskin, 1986), contrast thresholds are elevated about fourfold in acrylamide-treated monkeys at this spatiotemporal frequency. Such an elevation of contrast threshold would produce a progressively smaller effect on contrast discrimination as base contrast was raised, which was seen in our data (Fig. 5), and has been demonstrated in human thresholds, when contrast threshold was raised by testing contrast discrimination at eccentricities from 0–20 deg (Legge & Kersten, 1987).

These results demonstrate that normal contrast discrimination is possible in the absence of the P pathway. It seems unlikely that the residual performance could have been mediated by spared P cells in the far periphery, since the extremely low peripheral acuity of the acrylamide-dosed monkeys (Fig. 4) makes it clear that the cycle/deg stimulus, used to generate the data shown in Fig. 5, could probably only be resolved within the central visual field.

**Vernier acuity**

The high resolution of positional acuities, often termed "hyperacuities" because of the size of thresholds is below that of resolution thresholds measured under similar conditions, has prompted much theoretical analysis of what anatomical and physiological substrates could underlie them. One prominent view is that hyperacuities are limited not by the characteristics of retinal or thalamic pathways, but rather by constraints imposed by cortical processing (Levi et al., 1985). An alternative view is that retinal and cortical magnification are actually almost identical (Wäsßle et al., 1989), and that hyperacuities are limited by retinal processing (Banks et al., 1987). Neither of these approaches make strong predictions about the relative importance of P and M pathways in hyperacuity, but other analyses have attempted to relate positional acuities to the features of P and M pathways. Parker and Hawken (1985) measured the contrast sensitivity of single cells in macaque striate cortex, and calculated the positional sensitivity these cells would show if phase difference thresholds corresponded to a constant change in firing rate. Cells in cortical layer IVCa, the magnocellular recipient layer, show higher contrast sensitivity than those in IVCb, the parvocellular recipient layer, and thus, had smaller calculated positional sensitivity. This analysis suggested that the high sensitivity of individual neurons in the magnocellular path-
way might provide an advantage for this pathway in mediating hyperacuities. On the other hand, our demonstration that the parvocellular pathway mediates the very high contrast sensitivity that is found under conditions of low temporal frequencies (Merigan et al., 1991) might support exactly the opposite conclusion, i.e. that the parvocellular pathway dominates vernier acuity. In a recent paper (Wehrhahn & Westheimer, 1990), it was demonstrated that vernier acuity is contrast independent above contrasts of about 0.2, but that thresholds could be measured at contrasts as low as 0.04. The authors concluded that such vernier thresholds probably depend on the magnocellular pathway (following the same reasoning as Parker & Hawken, 1985), but that the parvocellular pathway might play a role under other conditions.

The results shown in Fig. 7 for monkey 310 demonstrate that vernier acuity, under the conditions of this experiment, can be mediated, without loss, by the M pathway. The retina of this monkey is not described in the anatomical figures of this paper because they were not stained with the Gros-Schultze stain for M cells. However, we know that P pathway neurons in this monkey were virtually destroyed over the central retina from Nissl stains of retinal wholemounts from this monkey (see Results) as well as from cytochrome-oxidase staining of its lateral geniculate (Lynch et al., in preparation). While some P cells were preserved in the far periphery of the retina in this monkey, the vernier acuity measured here is too high to be mediated by peripheral vision (Westheimer, 1982). On the other hand, we do not know why vernier acuity was lower than that of controls in monkey 117, despite rather complete preservation of M cells (Fig. 3). This monkey received extended training on this task, and her elevated thresholds were very reliable. We can only suggest that the vernier acuity task, in which misalignment could be presented in either direction, was a difficult task for this monkey.

We could not establish in this study whether normal vernier acuity performance could be mediated by the P pathway alone, a possibility that therefore remains viable. It may be that the relative importance of P and M pathways in vernier acuity depends on the stimulus conditions used. For example, the stimuli in this study were of extremely low luminance, and this could have canted detection towards the M pathway (Purpura et al., 1988). On the other hand, vernier acuity for isoluminant color targets (Krauskopf & Farell, 1991; Morgan & Aiba, 1985) may be mediated by the P pathway, since we have shown that chromatic vision appears to depend only on the P pathway (Merigan, 1989; Merigan et al., 1991b). Finally, positional acuity for the localization of Gabor patches (Toet & Koenderink, 1988) may be dominated by P or M pathways depending on the spatial frequency of the sinusoidal component of the Gabor. Thus, at the present time it appears prudent to assume that neither M nor P pathways are exclusive mediators of vernier acuity, but that the size, chromaticity, luminance, and spatiotemporal content of the stimulus may alter the relative role of the two pathways in vernier acuity.

**Form discrimination**

Identification of the P pathway with form discrimination derives largely from the anatomical finding that the P pathway provides a major input to areas V4 and inferotemporal cortex, both of which have been implicated in form perception (Gross, 1972; Heywood & Cowey, 1987). It is, of course, entirely possible that the P pathway is not uniquely important for form perception, given the high level of anatomical crosstalk that has been found in visual cortex (see DeYoe & VanEssen, 1988, for a review), and in particular the evidence that cortical area V4 appears to receive input from both parvocellular and magnocellular pathways (Ferrera et al., 1991). If, on the other hand, the P pathway were essential to form perception in the normal primate, we might find some degradation in form recognition, even under the present conditions of testing months after a P pathway lesion was produced.

However, the form-discrimination results of this study suggest that integrity of the P pathway is not necessary for form discrimination at least as tested with the present stimuli. The possibility that monkey 310 used the far periphery of the visual field, where some P cells were preserved, for these discriminations is rendered unlikely by its performance on stimulus 3 which subtended only 0.54 deg vertically, and is difficult to resolve in the far periphery. These results must be interpreted with some care, however. One possible conclusion is that form perception might have been affected at an earlier point in time, but that the plasticity of the nervous system permitted substitution of the previously ineffective magnocellular system for this function. While one cannot rule out this hypothesis, we do not favor it because the other visual effects of damage to the parvocellular pathway appear permanent (Merigan, 1989). A second possibility is that the acrylamide-dosed monkey actually has a slight form-discrimination deficit relative to its own ability prior to acrylamide exposure, but that this did not show up because we did not match experimental and control monkeys for form-discrimination ability prior to acrylamide exposure. This possibility cannot be dismissed in the context of the present study, although our results do suggest that any form-perception deficit produced by acrylamide exposure could not have been very large. Finally, the possibility which we favor is that the parvocellular pathway is not critical to performance of the form-discrimination tasks examined here. Such an interpretation would be consistent with the findings of Schiller and co-workers (Schiller et al., 1990b) as well as with our previous conclusion that the P or M pathway alone could mediate many complex visual-discrimination abilities if only the stimuli used to test these abilities can be well transmitted by the pathway of interest (Merigan, 1991b).

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**References**


