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Cortical Representation of a Myopic Peripapillary Crescent

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Abstract

Purpose—To determine how formation of an acquired myopic crescent adjacent to the optic disc affects metabolic activity in the primary visual cortex.

Design—Laboratory animal study.

Participants—Three macaque monkeys.

Methods—The blind spot region in the primary visual cortex was labeled by cytochrome oxidase histochemistry or [³H]proline autoradiography.

Main Outcome Measures—Visualization of the representation of the blind spot and myopic peripapillary crescent in the visual cortex.

Results—In high myopia, a region resembling the myopic peripapillary crescent was visible in cortical sections processed for cytochrome oxidase. In this region, metabolic activity was reduced in ocular dominance columns that normally would be driven by input from retina corresponding to the myopic peripapillary crescent.

Conclusions—The formation of a myopic crescent is accompanied by loss of metabolic activity in cortex supplied by the affected retina. This observation confirms that retinal tissue is damaged by the development of a myopic crescent, rather than simply translocated in a temporal direction. The cortical defect matches the myopic peripapillary crescent in size and shape, indicating that there is no “fill-in” of the retinotopic map by healthy, surrounding retina.

INTRODUCTION

The optic disc in each eye gives rise to a natural scotoma, the blind spot. In the primary striate visual cortex the contralateral eye's blind spot appears as an oval region, centered at 15° along the representation of the horizontal meridian.¹ The alternating pattern formed by the ocular dominance columns is interrupted in this zone, because one eye contributes no

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input. In humans with a history of vision loss in one eye, the blind spot can be labeled at autopsy by processing the cortex for cytochrome oxidase (CO), a metabolic enzyme.^{2, 3} In animals it can also be labeled by transneuronal autoradiography after [³H]proline injection into one eye.⁴ At birth the blind spot representation is already present, indicating that it is “hard wired” into the cortex.⁵

Subjects with high myopia from axial elongation usually develop a crescent-shaped region of peripapillary temporal atrophy, sometimes with tilting of the optic disc.⁶⁻⁸ There are no photoreceptors in this atrophic zone, and partial or complete absence of other retinal layers.⁹⁻¹² Consequently, the blind spot becomes enlarged.^{13, 14} This phenomenon has been described in monkeys, as well as in humans.¹⁵ However, it is unknown whether enlargement of the blind spot, a process that occurs after the critical period for plasticity of ocular dominance columns, can be detected in the primary visual cortex.¹⁶ Here we describe the cortical representation of the blind spot in three macaque monkeys. Two animals were normal, but the third had acquired peripapillary atrophy from high myopia.

METHODS

Experiments were conducted in 3 adult male macaques, who were engaged in unrelated neurophysiological studies in our laboratory. All procedures followed protocols approved by the UCSF Institutional Animal Care and Use Committee. To ensure correct refraction for neurophysiological testing, the animals underwent periodic streak retinoscopy after dilation of the pupils with 1% cyclopentolate and 2.5% phenylephrine.

The neurophysiological studies were followed by histological examination of striate cortex. In two animals 2 mCi of [³H]proline in 30 µl of sterile saline were injected intravitreally to label the cortical ocular dominance columns. In one animal the columns were double-labeled by reacting the cortex for CO activity after enucleation of one eye. All procedures were performed under local and general anesthesia, and the animals were treated afterwards with an analgesic, buprenorphine (0.02 mg/kg).

For processing of brain tissue, the animals received a lethal dose of pentobarbital intraperitoneally and were then perfused transcardially with 1 L saline followed by 1 L 0.5% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4). Striate cortex was removed, unfolded, flattened, and cut tangentially to the pial surface with a freezing microtome. Individual 30 µm sections were mounted on slides for autoradiography or CO histochemistry.¹⁶ Digital photographs were taken of each section. Cortical layer 4C, containing the ocular dominance columns, was reconstructed by montaging serial images using Photoshop CS (Adobe Systems, San Jose, CA).

RESULTS

The pattern of metabolic activity revealed by levels of the mitochondrial enzyme, CO, was examined in the vicinity of the blind spot representation in striate cortex of three monkeys.

Monkey 1

This animal had a stable refraction of +0.50 sphere in each eye measured repeatedly by streak retinoscopy. The optic discs were normal, with no evidence of a peripapillary crescent. The ocular dominance columns were labeled by injection of [^3H]proline into the left eye and by enucleation of the right eye. The animal survived for 10 days after these procedures. This was necessary for transport of [^3H]proline to the primary visual cortex, via synapses in the lateral geniculate nucleus. It also allowed sufficient time for cortical levels of CO to change after enucleation of the right eye.

Ocular dominance columns were present in CO montages of layer 4C, owing to reduction of metabolic activity following loss of the right eye. In the left striate cortex, columns were present everywhere, except in the regions corresponding to the monocular crescent and the blind spot of the right eye (Fig 1A). The latter appeared as a solid dark oval, where columns were absent (Fig 1B). The intensity of CO activity within the blind spot representation was equal to the level present in the surrounding ocular dominance columns of the left eye. The blind spot representation was about 3-4 pairs of columns wide.

A montage from alternating histological sections prepared for autoradiography showed the distribution of [^3H]proline from the left eye (Fig 1C). The tracer, which appears bright in darkfield images, matched the distribution of dark CO activity in the cortex. This finding confirmed that the ocular dominance columns were labeled reliably by CO histology, and that the dark columns served the intact left eye. The region corresponding to the blind spot of the right eye was filled exclusively by [^3H]proline-labeled geniculate afferents belonging to the left eye. Consequently, it continued to show dark CO activity after removal of the right eye, because the right eye contributes no input to this zone.

Monkey 2

This animal had a refraction of plano OU and normal optic discs. The ocular dominance columns were labeled by [^3H]proline injection into the right eye, but no enucleation was performed. CO staining appeared uniform in density throughout layer 4C, because both eyes were intact, and hence they continued to drive normal cortical activity. Even in cortex containing the representation of the right eye's blind spot, CO activity was uniform (Fig 2A). This region was identified by examining autoradiographs prepared from alternating sections, which revealed a large oval region lacking [^3H]proline label, surrounded by ocular dominance columns (Fig 2B). The blind spot representation was unlabeled because [^3H]proline was injected into the contralateral right eye, rather than into the ipsilateral left eye, as in Monkey 1. This experiment showed that although the optic disc representation in cortex is supplied by only one eye, it contains a level of metabolic activity (reflected by CO staining) equal to that of surrounding cortex, where input is present from both eyes.

Monkey 3

This animal had a refraction of +0.50 OU at age 2 years. By age 4, his refraction was -3.50 OU. At age 6 years, when his refraction reached -10.50 OD and -10.00 OS, fundus pictures were taken because his myopia was so unusual. The right optic disc was tilted, and bordered temporally by a zone of peripapillary atrophy nearly half the width of the optic disc itself

(Fig 3A). At age 8 years, when the visual cortex was examined, the refraction was -12.50 sphere OD, -13.75 sphere OS.

In the left visual cortex there was a crescent-shaped zone where a few pairs of alternating dark and light ocular dominance columns were visible (Fig 3B). The dark and light columns were about equal in width. The density of the dark columns matched the background level of cortical CO activity. The ocular dominance columns were situated in the retinotopic map at exactly the location in striate cortex where the temporal side of the right optic disc is represented (Fig 3C). The most likely inference is that peripapillary damage from high myopia caused loss of retinal drive, resulting in down regulation of metabolic activity within the ocular dominance columns serving the right eye in the corresponding region of cortex.

DISCUSSION

The mechanism underlying the development of myopia is unknown. The spontaneous occurrence of progressive high myopia in a monkey performing daily visual tasks over years is exceedingly rare, although near work and restricted visual space may promote globe elongation.¹⁷ In the animal reported here, high myopia led to formation of a typical zone of peripapillary atrophy.¹⁸ Although the visual fields were not tested, it seems likely that peripapillary atrophy caused enlargement of the physiological blind spot, just as it does in humans.¹⁹ In the primary visual cortex, a metabolic correlate of this zone of myopic peripapillary atrophy was discovered. It consisted of a crescent, measuring about 2° horizontally by 6° vertically, adjacent to the optic disc representation (Fig 3). The crescent was rendered visible by loss of CO activity in ocular dominance columns that would normally be activated by retina corresponding to the peripapillary atrophy in the contralateral eye.

The site of the normal blind spot representation has been located in human visual cortex using functional magnetic resonance imaging.²⁰ It is unclear if this technique has sufficient spatial resolution to detect an enlarged blind spot caused by myopic peripapillary atrophy. It was identified in the monkey described here because the CO technique reveals patterns of metabolic activity at a histological level of resolution, superior to that attainable with non-invasive neuroimaging.²¹

The ocular dominance columns induced by peripapillary atrophy were equal in width (Fig 3B). In the macaque, visual loss during the critical period causes the columns of the affected eye to shrink, and those of the normal eye to expand. In the macaque the critical period for changes in column width is over by age 3 months.¹⁶ In this monkey, peripapillary atrophy developed after age 2 years, when the deprived columns were no longer vulnerable to shrinkage. For this reason they appeared pale, but not reduced in relative width.

In myopia it has been hypothesized that temporal stretching may expose the inner sleeve of the scleral canal, causing a zone resembling peripapillary atrophy to appear on the retinal surface (Fig 4). According to this model, the region thought to be atrophic may never have contained retinal tissue, because it once constituted the inner lining of the scleral canal.⁷ Our findings argue against this idea. If a peripapillary crescent arose simply by temporal

dragging, opening up a gap between the optic disc and the retina, no ocular dominance columns would become visible in the cortex. The fact that CO activity is reduced in the visual cortex strongly implies that retinal tissue is actually destroyed, not just translocated, by formation of a peripapillary crescent.

It has been reported that the visual field map in striate cortex is plastic, so that after a lesion occurs in the retina, cortical activity can be sustained by healthy retina outside the lesion.²²⁻²⁴ In macular degeneration, for example, re-organization of the map has been described, which allows peripheral retina to drive responses where normally the macula is represented.²⁵ However, subsequent studies have not found evidence for widespread plasticity in the visual field map.^{26, 27} If such plasticity is present, it might be subtle, allowing remapping over only a small distance. In that respect, peripapillary atrophy provides an ideal, natural lesion to probe for small amounts of cortical map plasticity. If loss of input could be “filled-in” by a shift in the retinotopic map, so that healthy retina beyond the zone of peripapillary atrophy could drive activity, then no ocular dominance columns would be visible in the cortex. The fact that ocular dominance columns were found to be present, in an area that corresponded exactly to the shape and size expected for the cortical representation of the myopic peripapillary crescent, suggests that scant topographic reorganization occurs after acquired retinal lesions.

Peripapillary atrophy from myopia is not a rare condition. Although it is a shame to think of brain tissue going to waste, our findings indicate that every myopic person with peripapillary atrophy harbors a small region in the primary visual cortex, where a few columns of cells sit metabolically idle due to loss of retinal drive.

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Figure 1.

Monkey 1. Double-labeling of the cortical optic disc representation. **A**, Montage of flattened layer 4C of left striate cortex showing ocular dominance columns labeled by CO after enucleation of the right eye. F = fovea, MC = monocular crescent. **B**, Boxed region above, centered on the optic disc representation of the right eye. **C**, Montage of alternate sections, showing bright label after transneuronal transport of [³H]proline from the left eye, which coincides with dark CO in (**B**). The right eye's blind spot representation is supplied only by the left eye.

Figure 2.

Monkey 2. Equal metabolic activity in the blind spot representation and surrounding binocular cortex. **A**, Left striate cortex centered at 15° along the horizontal meridian, showing uniform CO activity in a normal monkey with both eyes intact. **B**, Same region, labeled after [³H]proline injection into the right eye. The optic disc representation appears as a dark oval. It has the same level of CO activity as surrounding binocular cortex, which contains ocular dominance columns.

Figure 3.

Monkey 3. Cortical representation of myopic peripapillary atrophy. **A**, Right optic disc with temporal peripapillary atrophy, caused by high myopia. **B**, Left striate cortex, showing a crescent shaped region where CO activity is reduced in the right eye's ocular dominance columns. **C**, Drawing of the ocular dominance columns visible within the boxed region, shown above right. Dotted oval indicates the approximate location of the representation of the right eye's blind spot.

Figure 4.

Competing theories to explain myopic peripapillary crescent formation. **A**, The normal optic disc, before myopia onset. Asterisk denotes edge of retina and pigment epithelium; circle marks a point just behind the lamina cribrosa. **B**, A myopic crescent may develop by lateral traction, translocating the inside of the scleral canal onto the surface of the fundus (arrow). In this scenario, anchor points (*, o) are dragged temporally, but no retinal tissue is lost.⁷ Alternatively, as shown in bottom panel, there may be no scleral migration (anchor points stay fixed) but retina next to the optic disc undergoes degeneration.