Nasotemporal Overlap of Retinal Ganglion Cells in Humans: A Functional Study

Jens Reinhard and Susanne Trauzettel-Klosinski

Purpose. A zone of overlap along the vertical retinal meridian where ipsi- and contralaterally projecting ganglion cells intermingle has been demonstrated histologically in nonhuman primates. The widening of the zone of overlap in the foveal region was thought to produce a foveal sparing extending 1.5° in the blind hemifield in human hemianopia. The functional relevance of the nasotemporal overlap is still unclear and cannot be shown definitely by conventional perimetry, because of insufficient spatial accuracy, light-scattering effects, and insufficient fixation control. Therefore, this study was undertaken to investigate the vertical field border by a perimetric method that does not have these shortcomings.

Methods. A scanning laser ophthalmoscope (SLO) was used to scan vertical triplets of dots along the vertical field border in 20 patients (36 eyes) with homonymous hemianopia without macular sparing. Stimuli and fundus were imaged simultaneously for fixation monitoring.

Results. None of the patients showed a field border that coincided exactly with the vertical midline. In 34 eyes, the seeing area extended from the vertical meridian into the blind hemifield and formed a vertical strip of perception. None of the patients showed additional foveal sparing. Twenty-two eyes showed a concave shape of the seeing area within the foveal region of the blind hemifield.

Conclusions. Our results show that the nasotemporal overlap exists in humans. It consists of a strip of intact perception reaching into the blind hemifield. The concave shape can be explained by the size and distribution of the receptive fields of the retinal ganglion cells. (*Invest Ophthalmol Vis Sci.* 2003;44: 1568–1572) DOI:10.1167/iovs.02-0313

Macular sparing, a seeing area of 2° or more within the foveal region of the blind hemifield in hemianopia, has been controversial for a long time. We have shown in a previous study[1] by means of our own specially designed scanning laser ophthalmoscope (SLO) microperimetry that macular sparing exists and is no perimetric artifact. This perimetry allows measurement of the absolute field defect in the central visual field with up to 10° eccentricity with 0.5° horizontal and 1° vertical spatial accuracy. Stimuli and fundus were simultaneously imaged and recorded on videotape. Fixation was directly monitored during examination and evaluation. In four patients, we found macular sparing ranging from 2° to 5°.[1] The existence of macular sparing was explained with a double blood supply of the occipital pole[2,3]—that is, an anastomosis between the posterior and middle cerebral artery that leads to a sparing of the occipital pole in the case of ischemic lesions of the occipital lobe. Thus, macular sparing is a phenomenon of cortical origin.

The purpose of the present study was to investigate the existence of a different phenomenon called foveal sparing.[4] Histologic and histochemical studies in monkeys showed a zone where ipsi- and contralaterally projecting ganglion cells intermingle along the vertical retinal meridian.[5–9] In the foveal region, a widening of this zone was observed. This widening was supposed to cause a foveal sparing of approximately 1.5° extent within the hemianopic field defect if this phenomenon existed also in humans. Stone et al.[5] cut one optic tract and observed the areas of degeneration on the retina. They found a strip of intermingling ganglion cells along the vertical meridian that ranged 0.5° into each hemifield (Fig. 1A). Bunt et al.[6] and Bunt and Minckler[7] used a retrograde labeling technique in monkeys and confirmed the finding by Stone et al.[5] in principle, but in the foveal region they found the strip to be widened by up to 1.5° toward either side (Fig. 1B). Fukuda et al.[9] found the overlap increasing from 0.3° in the central retina and gradually widening toward the periphery (Fig. 1C).

The functional consequences of these morphologic findings are still unclear. Stone et al.,[5] Bunt et al.,[6] and Bunt and Minckler[7] pointed out that the receptive fields of the ganglion cells cannot be derived from their morphologic positions. Leventhal et al.[8] and Fukuda et al.[9] concluded that foveal sparing exists in the visual field of patients with hemianopia. Huber[4] investigated 11 patients with occipital lobectomy due to brain tumors. The occipital pole—the part of the optical pathway that is considered to produce the macular sparing—was removed together with the whole occipital lobe. Huber[4] performed Goldmann perimetry assessing carefully the vertical field border. As expected, no macular sparing extending several degrees was found in these patients. He found, however, that the hemifield defect comes no closer to the fovea than 1° in all patients.[4] Huber[4,10] concluded that the seeing area extends 0.5° into the blind hemifield along the vertical meridian and in the foveal region 1.5° to 2°.

In our previous study[1] we looked for macular sparing in patients with hemianopia. We found four patients with macular sparing extending 2° to 5° horizontally and a vertical strip of overlap of 0.5° to 1° in 12 of 13 eyes, but our results allowed no definite conclusions regarding foveal sparing because of the small sample size.

The existence of foveal sparing cannot be shown by conventional perimetry, because of insufficient fixation control, the effects of light-scattering, and insufficient spatial accuracy. For instance, eye movements during stimulus presentation cause a shift of the entire vertical field border. A common fixation pattern of patients with hemianopia is characterized by frequent saccades toward the hemianopic side.[1,11] In addition, some patients without macular sparing use an eccentric retinal locus for fixation, which also causes a shift of the visual field border in conventional perimetry.[1,12]

From the Department of Pathophysiology of Vision and Neuroophthalmology, University Eye Hospital Tübingen, Tübingen Germany.

Supported by German Research Council Grants DFG Zr 1/13-1 and DFG Zr 1/14-1 and fortüne 294, an intramural research program.

Submitted for publication April 1, 2002; revised November 1, 2002; accepted November 19, 2002.

Commercial relationships policy: N.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Corresponding author: Jens Reinhard, Department of Pathophysiology of Vision & Neuroophthalmology, University Eye Hospital of Tübingen, Schleichstrasse 12-16, D-72076 Tübingen, Germany; jens.reinhard@med.uni-tuebingen.de.

Investigative Ophthalmology & Visual Science, April 2003, Vol. 44, No. 4

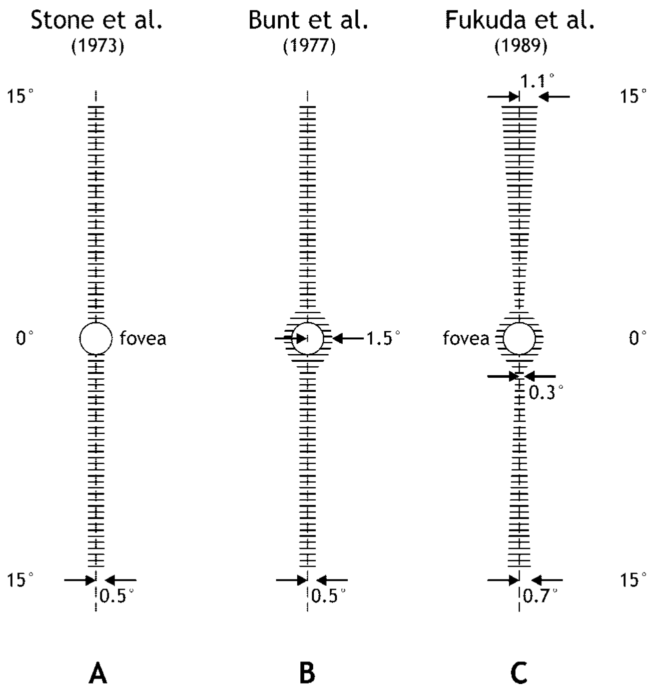

FIGURE 1. Synopsis of results regarding areas of intermingling retinal ganglion cells in monkeys. The results of three experiments in monkeys are shown. *Centered circle*: the foveal region, where only a few ganglion cells are located; *dashed line*: vertical meridian. Stone et al.[5] found a strip of intermingling ganglion cells reaching 0.5° to each side (**A**). Bunt et al.[6] found it widening in the foveal region (**B**), and Fukuda et al.[9] found it widening additionally from 0.3° toward the retinal periphery (**C**). The widening was more pronounced in the upper part of the retina (1.1° vs. 0.7°).

The spatial accuracy of standard automated grid perimetry techniques is too low to detect foveal sparing, and kinetic procedures potentially induce the patient to look toward the stimulus. In addition, light-scatter reduces the spatial accuracy, especially in the center of the visual field (described in the Methods section). The purpose of this study was to determine the exact shape of the vertical border of the visual field by a method that avoids these influences, to examine the functional relevance of the histologic data in humans and to clarify whether foveal sparing exists.

METHODS

We used an SLO (Rodenstock Instruments, Munich, Germany) to image the fundus and to present stimuli simultaneously using an acousto-optic modulator. This allows determination of the exact position of the foveola in relation to the fixation target and stimulus.

To investigate the shape of the absolute visual field defect we performed a specially designed microperimetry in 20 patients with hemianopia. We scanned vertical triplets of black dots on a bright red background in different eccentricities from the vertical meridian and distances to each other onto the patient's retina[1] (Fig. 2A). In central fixation, the vertical and the horizontal meridians cross the fovea, and the foveolar reflex is identical with the center of the fixation cross. The presentation time was 120 ms, and the Michelson contrast was 0.986. The triplets ($n = 113$) consisted of three dots of 20 minarc diameter (Fig. 2A). The middle dot was always located on the horizontal meridian. On the vertical meridian, only the upper and the lower dots were presented, to avoid interfering with the fixation cross.

All triplets together formed a grid with 0.5° horizontal and 1° vertical spatial accuracy. The grid had a vertical extent of 16° (±8°) and a horizontal extent of 11° (1° toward the seeing hemifield and 10° toward the blind hemifield, Fig. 2B). Caused by the triplet configuration, the dots on the horizontal meridian were tested eight times up to 3° eccentricity and five times at higher eccentricities in each eye. The testing procedure concentrated on the foveal area to prevent missing an area of foveal sparing. The data from the more peripheral part (4°–8°) of the visual field along the vertical meridian are of minor significance. Furthermore, the retinal periphery could not be investigated because of the technically restricted SLO field of ±8° vertical eccentricity.

The SLO method allows observation of the stimuli and the fundus simultaneously on a video monitor. The entire recording was stored on a SVHS videotape.

During the examination, the patients had to fixate a cross of 20 minarc diameter in the SLO. When the patient fixated the cross foveally, the investigator presented one triplet, and the patient was asked to report whether he or she saw any of the three presented dots and if so, which of them (the upper, the lower, and/or the middle). Because the middle dot was always located on the horizontal meridian, it was easy for the patient to localize the position of the dots. If fixation was unstable during the trial, the investigator repeated the last presentation. The eccentricity of the dots and their distance to each other was varied in random order.

During off-line analysis of the videotape, the position of three to four small retinal vessels taken from a still picture with central fixation was marked once on the video screen. Subsequently, the video se-

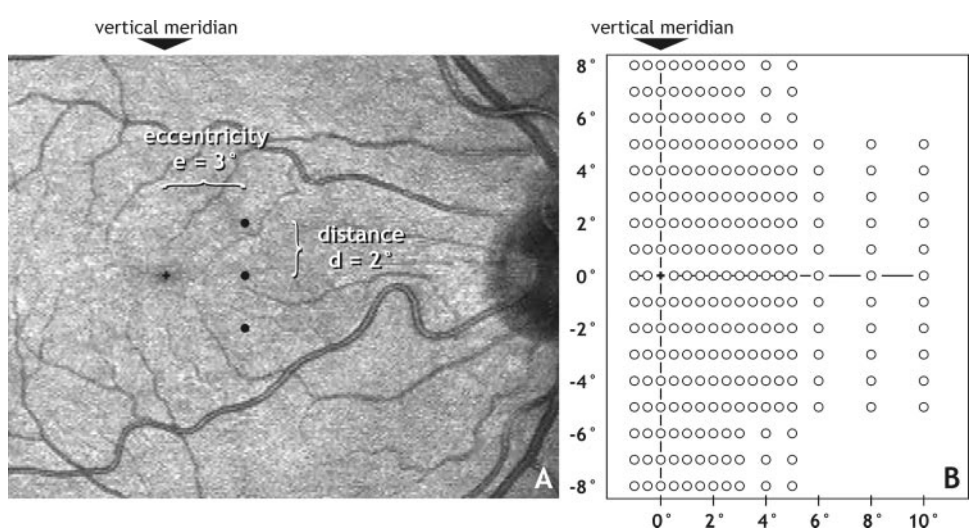

FIGURE 2. (**A**) Stimuli and fundus are simultaneously visualized by the SLO. Vertical triplets of dots are scanned onto the retina at various eccentricities from the vertical meridian and distances to each other. (**A**) Example of a triplet with 3° eccentricity, 2° distance, and 120-ms presentation time. The investigator monitored fixation of the patient during presentation and in the off-line evaluation. Altogether, a grid comprising 241 locations in each eye was tested (**B**), 1° within the seeing hemifield, 10° within the blind hemifield, and ±8° vertical eccentricity. In this example, the test-point grid for testing right-side hemianopia is displayed schematically.

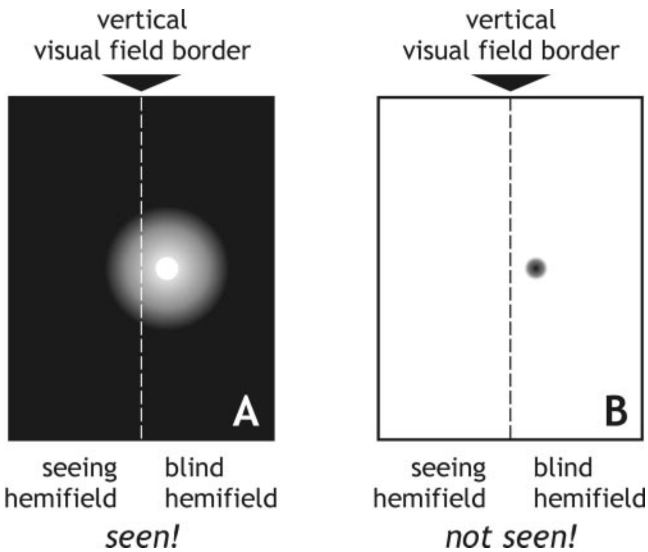

FIGURE 3. Effects of the stimulus conditions and light-scattering on the perception of stimuli near the vertical meridian. Schematic diagram of a patient with right-side hemianopia. (**A**) In the case of presenting a bright stimulus on a dark background, the scattered light causes a halo that extends to the seeing hemiretina. The patient sees the scattered light and returns a false-positive response. (**B**) The stimulus is inverted to dark on a bright background. The patient does not see the dot, because it causes no halo.

quences with the stimuli were watched in slow motion field by field. The duration of every stimulus sequence was 120 ms which corresponds to six video fields (three video frames). During each of these sequences, the position of the vessels in the video image in relation to the vessel marks on the screen was compared. If the patient's fundus was shifted during these 120 ms, the answer was discarded; otherwise, the seen dots were entered into an evaluation table. Even small retinal shifts of less than the diameter of a small retinal vessel (i.e., <5 minarc) could be detected. Eccentric fixation was excluded in all patients by carefully observing the position of the fovea and by admonishing them to fixate the center of the fixation cross when eye movements occurred. The patients' responses were highly reproducible, especially on the horizontal meridian, where multiple dots were tested. Inconsistent answers between trials never exceeded 2% of all test points per eye.

One important feature of our specially designed SLO perimetry is the elimination of eye movement artifacts during stimulus presentation as well as during off-line evaluation. The second beneficial feature of our SLO microperimetry is the reduction of light-scattering by the stimulus itself (Fig. 3). In conventional perimetry, even slight lens opacities produce a halo when a bright stimulus on a darker background is presented (Fig. 3A). If the stimulus is located within the field defect, near the border to the seeing hemifield, the halo may cause a false-positive response, because the patient sees part of the halo. This effect is more pronounced in the foveal region because of its high sensitivity and may lead to a false finding of foveal sparing. Therefore, we used the SLO in inverted mode (dark stimuli on bright background, Fig. 3B) where the light is scattered into the stimulus.

Patients

We investigated 20 patients (36 eyes) with homonymous hemianopia (9 right-side and 11 left-side; 9 men, 11 women; mean age, 43.9 ± 13.9 years). All patients underwent a complete neuro-ophthalmologic and visual field examination (Tübingen Automated Perimetry). Five patients had cerebral vascular insults, four had brain tumors, six traumas, one meningoencephalitis, two intracerebral hemorrhage, and two arteriovenous malformations. In all cases, the diagnoses were confirmed by brain imaging (computed tomography [CT] and/or magnetic resonance imaging [MRI]). The mean time since onset was 5.2 ± 6.9 years. Patients with macular sparing (2° or more) or with visual field defects in both hemifields were excluded. (Macular sparing would hide an area of foveal sparing that would be expected to be smaller.) This research followed the tenets of the declaration of Helsinki, and informed consent was obtained from the subjects after explanation of the nature and possible consequences of the study.

RESULTS

In all patients, the border of the hemianopic absolute visual field defect could be determined with a horizontal accuracy of 0.5° and vertical accuracy of 1°. None of the patients showed a border that coincided exactly with the vertical meridian. In 34 of 36 eyes, the seeing area extended at least 0.5° toward the

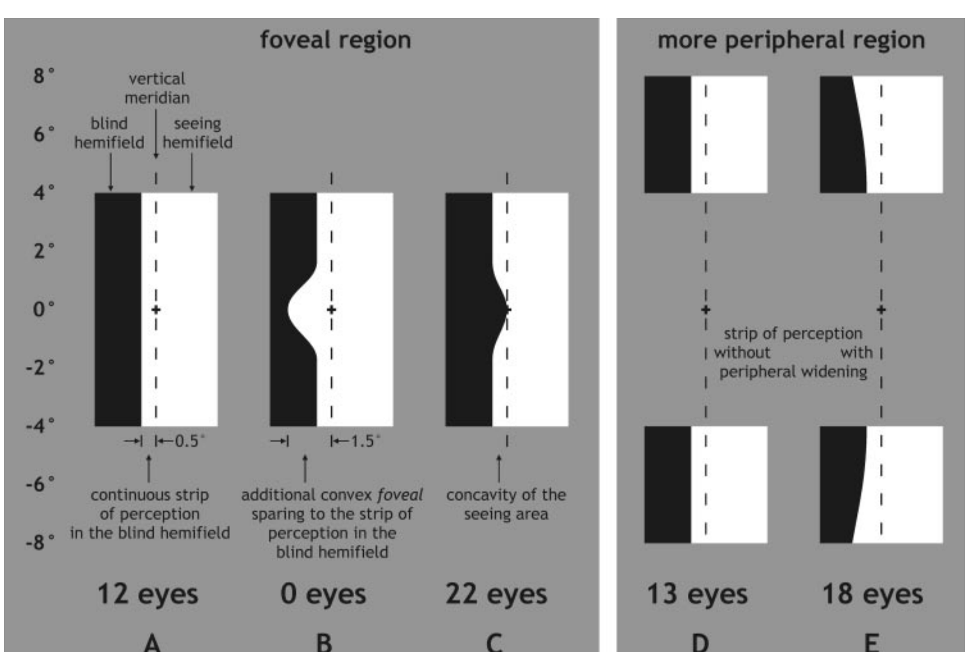

FIGURE 4. Results of the SLO investigations in the foveal area (**A**–**C**) and in the more peripheral region (4°–8° vertical eccentricity; **D**, **E**). A straight strip of perception along the vertical meridian within the blind hemifield was found in 12 eyes (**A**). Foveal sparing—that is, a central visual field convexity extending 1.5° added to the vertical strip of perception in the blind hemifield—was not found in any of the patients (**B**). In 22 eyes, a concave shape of the strip of perception occurred (**C**). In the more peripheral region, 13 eyes showed a straight line of perception along the vertical meridian (**D**). In 18 eyes, this strip widened toward the periphery (**E**).

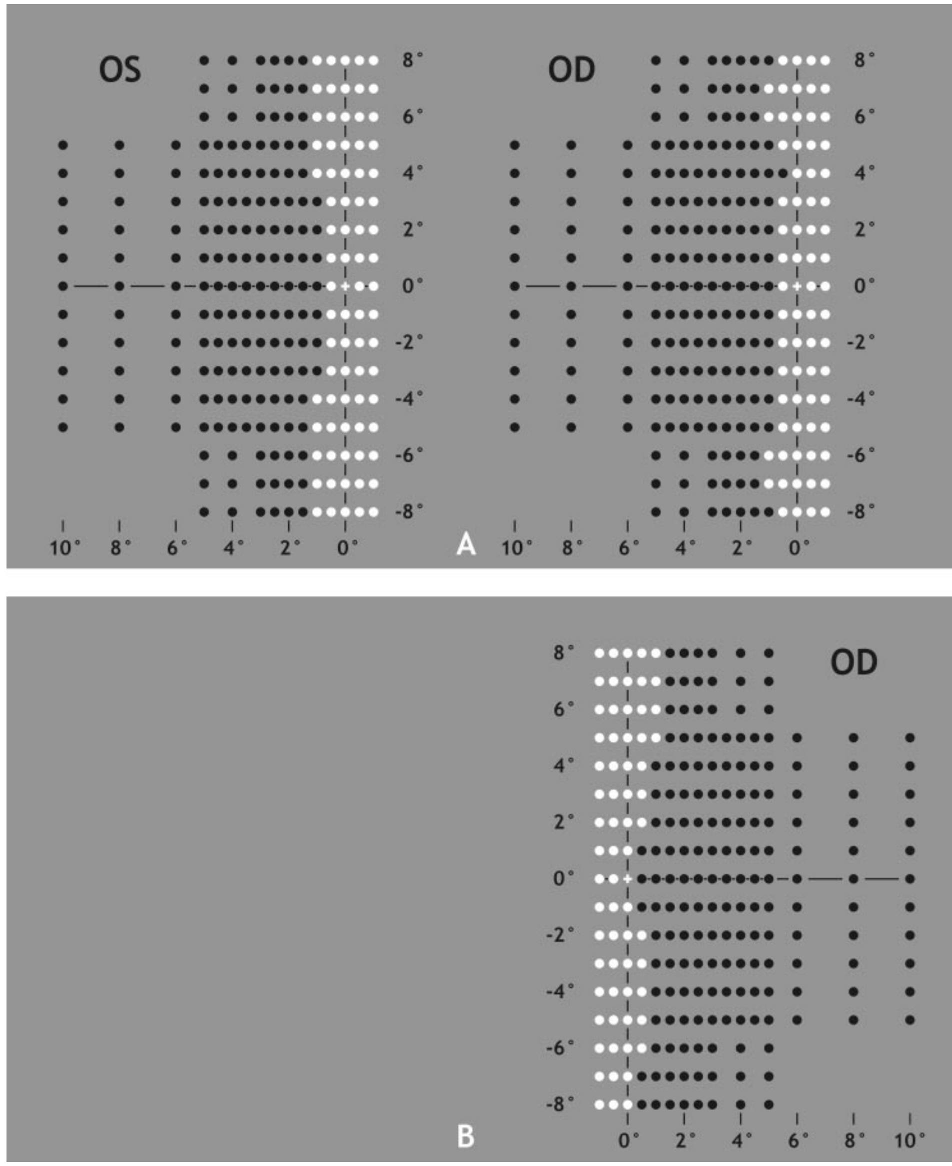

FIGURE 5. Two original findings. *White dots*: seen by the patient; *black dot*: unseen; *dashed lines*: horizontal and vertical meridians. (**A**) Patient with left-side hemianopia had a continuous, straight strip of perception in the foveal region, widening in the periphery. Fixation was definitely central. (**B**) Patient with right-side hemianopia showed concavity of the visual field in the foveal region, with a strip of perception that was more pronounced in the upper visual field, which may be the consequence of slight ocular torsion. The patient's left eye was blind.

hemianopic side and formed a sometimes incomplete vertical strip of perception within the blind hemifield along the vertical meridian. In 12 eyes, the border of the strip of perception in the hemianopic field was a straight line (Fig. 4A). Foveal sparing—a central visual field convexity added to the vertical strip of perception—did not occur in any eye (Fig. 4B). In 22 eyes, however, this strip of perception narrowed in the foveal area—resulting in a concave shape of the seeing part of the visual field—that is, a dent instead of a convex area of sparing (Fig. 4C).

In the more peripheral region (4°–8°), the border of the perceptual strip was a straight line in 13 eyes (Fig. 4D) and showed a widening in 18 eyes (Fig. 4E). In three eyes, the peripheral shape was not definitely determinable.

Figure 5 shows two original findings. The seen dots are white, the unseen dots are black. The graph shows the complete stimulus grid. The first patient (Fig. 5A) had left-side hemianopia. Along the vertical meridian, there was a strip of perception of 0.5° in the foveal area with a slight widening of 1° in the more peripheral area. The second patient (Fig. 5B) had right-side hemianopia. The border in the foveal region was concave without any overlap at the horizontal meridian. At 2° vertical eccentricity, a strip of overlap began. Its asymmetric peripheral widening indicates a slight torsion of the fundus.

DISCUSSION

A vertical strip of perception along the midline was observed in 34 of 36 eyes. Additional foveal sparing to the strip of perception did not occur in any of our patients. The finding of a concave dent instead of a convex area of sparing does not necessarily mean an absence of any overlap in the foveal region, because our method has limited accuracy and cannot determine whether there is a very small area of sparing of some minutes of arc. The test point closest to the foveola was located 30 minarc beside the fixation point and had a diameter of 20 minarc. Hence, it cannot be ruled out that there is a very narrow strip of perception in the foveal region of less than 20 minarc.

In a clinical study, Huber,[4] using Goldmann perimetry, found in his patients with occipital lobectomy a widening strip of perception in the foveal region and called this phenomenon foveal sparing. He attributed his finding to a "checkerboard innervation" of the central part of the retina. A possible explanation of Huber's findings is the effect of light scattering of the stimuli in the Goldmann perimeter as described in the introduction (Fig. 3A). The patients may have seen the halos of the stimuli presented within the absolute scotoma, but very near to the vertical meridian, which led to the conclusion that foveal sparing had occurred. An additional factor may have been unstable and/or eccentric fixation.[1]

The distribution of ganglion cells in the foveal and perifoveal regions is of great interest regarding foveal sparing. Investigators in the histologic and histochemical studies[5–9] in monkeys assume that the overlap in the foveal region may cause foveal sparing in the visual field. In contrast, a hypothesis supporting the absence of foveal sparing was suggested by Wyatt,[13] who emphasized the difference between the anatomic locations of the ganglion cell bodies and the location of the associated receptive field, which may differ in the central retina. The ganglion cell bodies located at the foveal rim that contribute to the widening zone of intermingling ipsi- and contralaterally projecting ganglion cells have their corresponding receptive fields at and near the very center of the visual field. As a consequence of the histologically widening strip of intermingling ganglion cells and the enlargement of the receptive fields in the periphery, the shape of the seeing visual area should be concave with the smallest extent around the fovea. The findings of the present study concerning the narrowing of the strip of perception at the fovea confirm the hypothesis of Wyatt.[13]

Regarding the more peripheral region, Fukuda et al.[9] found the width of the strip of overlap increasing in the periphery. Our data confirm the results of Fukuda et al.[9] We found a peripheral widening of the vertical strip of perception extending at least 0.5° in 18 eyes. However, because of our technically restricted SLO field, we were able to test the visual field only within ±8° of vertical eccentricity. The shape of the more peripheral visual field border could not be determined. The asymmetry of the overlap, as described by Fukuda et al.,[9] could not be confirmed in this study.

Perry and Cowey[14] showed the importance of the length of the fibers of Henle in the retina of macaque monkeys. The fibers of Henle connect cones with the inner nuclear layer cells and subsequent ganglion cells. Because of the dense packing of foveal cones, the cells of the ganglion and inner nuclear layers are radially displaced, which means that the foveal cones have long Henle fibers. The Henle fibers radiate from the fovea in all directions. Some cones from a small patch of the center of the fovea can have their pedicles in the nasal and others in the temporal retina.

Perry and Cowey[14] further pointed out the relevance of the offset by the Henle fibers and the bipolar and ganglion cells, which is important in the relationship between the ganglion cells at the fovea and the central magnification factor. They found a total offset of 412 μm at a 300-μm distance from the foveal center, declining with increasing distance from the fovea. They showed that the central few degrees of the retina are disproportionately overrepresented in the visual cortex compared to more eccentric regions.[15]

This overrepresentation was later confirmed in brain lesion imaging and visual field studies in humans, where the central 10° of the visual field were found to be represented in more than 50% of the primary visual cortex.[2,3] The linear magnification factor—that is, the length of cortex that represents 1° of the visual field at a given eccentricity (e)—was calculated by Horton and Hoyt[2] in humans to $M_{\text{linear}}(e) = 17.3/(e + 0.75°)$. This means that, at 0.5° eccentricity, 1° of the visual field is represented by 13.8 mm of cortical length. A slight strip of perception in the hemianopic field due to a nasotemporal overlap of retinal ganglion cells therefore is represented in a highly magnified cortical area.

Another interesting aspect is the region of the developing optic chiasm, a ventral midline structure, where retinal ganglion cell axons diverge to either side of the brain. At this point, growing axons decide whether to cross and project contralaterally or to remain on the ipsilateral side of the brain. This guidance decision is regulated by guidance receptors, the roundabout receptor (Robo) and its ligand (Slit) which was shown in *Drosophila* and in mice.[16,17] These studies[16,17] show that this guiding systems play an important role in the chiasm formation. However, this decision for crossing or noncrossing at the midline of the chiasm has to be differentiated from the nasotemporal overlap at the retinal vertical meridian, which is the subject of this article.

Our study reconciles the results of the histologic and histochemical investigations in monkeys with the functional situation in humans.

Acknowledgments

The authors thank Manfred MacKeben, PhD, Smith Kettlewell Eye Research Institute (San Francisco, CA) for valuable comments on the manuscript.

References

1. Trauzettel-Klosinski S, Reinhard J. The vertical field border in hemianopia and its significance for fixation and reading. *Invest Ophthalmol Vis Sci.* 1998;39:2177–2186.
2. Horton JC, Hoyt WF. The representation of the visual field in human striate cortex. *Arch Ophthalmol.* 1991;109:816–824.
3. McFadzean R, Brosnahan D, Hadley D, Mutlukan E. Representation of the visual field in the occipital striate cortex. *Br J Ophthalmol.* 1994;78:185–190.
4. Huber A. Homonymous hemianopia after occipital lobectomy. *Am J Ophthalmol.* 1962;54:623–629.
5. Stone J, Leicester J, Sherman SM. The naso-temporal division of the monkey's retina. *J Comp Neurol.* 1973;150:333–348.
6. Bunt AH, Minckler DS, Johanson GW. Demonstration of bilateral projection of the central retina of the monkey with horseradish peroxidase neuronography. *J Comp Neurol.* 1977;171:619–630.
7. Bunt AH, Minckler DS. Foveal sparing: new anatomical evidence for bilateral representation of the central retina. *Arch Ophthalmol.* 1977;95:1445–1447.
8. Leventhal AG, Ault SJ, Vitek DJ. The nasotemporal division in primate retina: the neural bases of macular sparing and splitting. *Science.* 1988;240:66–67.
9. Fukuda Y, Sawai H, Watanabe M, Wakakuwa K, Morigiwa K. Nasotemporal overlap of crossed and uncrossed retinal ganglion cell projections in the Japanese monkey (Macaca fuscata). *J Neurosci.* 1989;9:2353–2373.
10. Huber A. Die homonyme Hemianopsie. *Klin Monatsbl Augenheilkd.* 1991;199:396–405.
11. Bischoff P, Lang J, Huber A. Macular sparing as a perimetric artifact. *Am J Ophthalmol.* 1995;119:72–80.
12. Trauzettel-Klosinski S. Eccentric fixation with hemianopic field defects: a valuable strategy to improve reading ability and an indication of cortical plasticity. *Neuro-ophthalmology.* 1997;18:117–131.
13. Wyatt HJ. Nasotemporal overlap and visual field sparing. *Invest Ophthalmol Vis Sci.* 1978;17:1128–1130.
14. Perry VH, Cowey A. The lengths of the fibres of Henle in the retina of macaque monkeys: implications for vision. *Neuroscience.* 1988;25:225–236.
15. Perry VH, Cowey A. The ganglion cell and cone distributions in the monkey's retina: implications for central magnification factors. *Vision Res.* 1985;25:1795–1810.
16. Erskine L, Williams SE, Brose K, et al. Retinal ganglion cell axon guidance in the mouse optic chiasm: expression and function of robos and slits. *J Neurosci.* 2000;20:4975–4982.
17. Mason CA, Sretavan DW. Glia, neurons, and axon pathfinding during optic chiasm development. *Curr Opin Neurobiol.* 1997;7:647–653.