Normal Retinotopic Mapping in Human Strabismus with Anomalous Retinal Correspondence

Glen McCormack

Burian proposed that a functional retinotopic remapping of the deviated eye on striate visual cortex may be the physiologic basis for the perceptual phenomenon of anomalous retinal correspondence (ARC) in human strabismus. This investigation searched for this type of retinotopic remapping in five esotropes and one exotrope with ARC by means of visual evoked potential (VEP) topographic mapping. Uniocular stimulation of thefoveas (corresponding points) during binocular vision in a normal subject yielded identical VEP scalp topographies from each eye. Stimulation of anomalously corresponding points produced different VEP scalp topographies from each eye in the six strabismic subjects. Uniocular stimulation of the anatomic foveas of each eye (noncorresponding points) in a strabismic subject during binocular vision produced identical VEP scalp topographies. These results suggest that there is no significant functional binocular realignment of retinotopic mapping in the visual cortex of human strabismics with ARC. Invest Ophthalmol Vis Sci 31:559-568, 1990

Anomalous retinal correspondence (ARC) is the difference of visual direction associated with foveal stimulation of each eye, or the common visual direction associated with stimulation of the fovea of one eye and a peripheral retinal locus in the fellow eye.1 ARC is found in strabismus and is of clinical significance because its presence is an impediment to the successful treatment of strabismus.2

Burian3 proposed that the retinotopic mapping of the deviated eye undergoes a physiologic shift in the striate cortex during binocular vision. I have called the hypothesized change of the deviated eye's retinotopic mapping in binocular vision the "ARC shift." This model assumes that retinotopic mapping in the visual cortex is the basis for the perception of visual direction. Anomalous retinotopic mapping due to ARC could not be anatomically fixed since the anomalous localization is significantly altered or eliminated by covering the normally straight eye. Visual evoked potential (VEP) studies have confirmed normal retinotopic mapping during monocular vision in common types of strabismus,4-6 including cases with ARC.4

Direct evidence for the ARC shift is lacking. A neuroanatomic substrate for the ARC shift is suggested by the results of Berman and Payne,7 who found that artificially induced squint in kittens prevents the reduction of dendritic arborization normally associated with maturation of the visual cortex. This type of anomaly makes it possible, theoretically, for binocular interaction to occur across cortical areas well beyond the normal range of binocular interaction, and thus perhaps account for the ARC shift. Schlaer8 reported having altered the modal value for preferred vertical disparity in binocular neurons of kitten visual cortex by means of vertical prism. He suggested that this vertical disparity shift may be similar to the mechanism of ARC. Schlaer's result could not be replicated by Van Sluyters.9

Campos10 argued that perceptual fusion in strabismic patients is evidence of ARC. Campos11 and Campos and Chiesi12 claimed to have shown objective evidence of fusion in patients with ARC through the binocular enhancement of the pattern VEP. Since the early components of pattern VEPs in humans probably arise from striate and parastriate cortical activity,13,14 Campos and Chiesi's results may be viewed as supporting the ARC shift hypothesis.

Since ARC is defined by visual direction criteria rather than by fusion criteria, the ARC shift hypothesis may be most directly tested by measurements related to visual direction. If retinotopic mapping in the visual cortex is the basis for the perception of visual direction,15 then the ARC shift may reveal itself in the topography of the VEP (the spatial distribution of VEP amplitude over the posterior scalp) since VEP topography is known to be correlated to retinotopic mapping in the visual cortex.13,14 If the deviated eye's foveal projections are physiologically
shifted so as to connect with peripheral cortex during binocular vision, then the VEP topography from stimulation of the fovea of the deviated eye should reflect a peripheral cortex origin. Similarly, stimulation of the peripheral retinal point of the deviating eye corresponding to the fovea of the dominant eye (termed here the "pseudofovea") should give rise to a foveal cortex VEP topography in binocular vision. In both cases, stimulation of the fovea of the straight eye during binocular vision is assumed to activate foveal visual cortex. The comparison of these VEP topography expectations to the visual direction percepts generated by the VEP stimuli should reveal an ARC shift.

Materials and Methods

Subjects

Five adult constant esotropes, one constant exotrope, and one normal subject were evaluated. The determination of anomalous correspondence was based upon three tests: the afterimage test, the striated glasses test, and the experimental amblyoscope used for VEP stimulation. All six strabismic subjects gave positive results on all three ARC tests. Persons with significant amblyopia (less than 20/30 Snellen visual acuity) were excluded for two reasons: 1) amblyopia potentially could distort VEP topography independently of any effects caused by ARC, and 2) stable fixation by each eye was necessary for accurate calibration of an eye movement monitoring system. Centricity of fixation was determined primarily by visuoscopy and was corroborated by the Maxwell’s Spot and Haidinger’s Brush tests. Since a discussion of clinical tests of binocular vision is beyond the scope of this report, the reader is referred to Burian and von Noorden for details. A brief clinical synopsis of each subject is shown in Table 1. Written informed consent was obtained from subjects after the procedures were fully explained.

Stimulus System

An experimental amblyoscope provided evoked potential stimulation on selected retinal sites in each eye. A 27° × 35° (height × width) background field of 0.9 fL luminance was viewed binocularly at 50 cm (Fig. 1A). The fixation point was a small Snellen letter placed at the intersection of the median plane of the subject’s head with the background field. A large “X” drawn on the periphery of the background field provided additional binocular stimulation. Tachistoscopes (Gerbrands, Arlington, MA) presented 9° × 2° stimulus fields of 2.3 fL luminance to each eye by way of Galvanometer-mounted beam splitter mirrors. Preliminary trials found that this stimulus field size was large enough to produce significant pattern-onset VEPs, yet sufficiently narrow to generate significant VEP topography changes with stimulus field displacements of 1° or less. Stimulus field position along the horizontal meridian could be independently controlled for each eye. Six-min wide nonius lines were visible in the upper half of the right eye’s stimulus field and in the lower half of the left eye’s stimulus field. The subject aligned these nonius lines to determine the subjective angle of deviation (Table 1).

Evoked potentials were elicited by pattern-onset of 24’ checks of 50% contrast. Preliminary trials found that this check size generated relatively reliable pattern-onset VEPs, yet sufficiently narrow to generate significant VEP topography changes with stimulus field displacements of 1° or less. Stimulus field position along the horizontal meridian could be independently controlled for each eye. Six-min wide nonius lines were visible in the upper half of the right eye’s stimulus field and in the lower half of the left eye’s stimulus field. The subject aligned these nonius lines to determine the subjective angle of deviation (Table 1).

Table 1. Clinical findings on the six strabismic experimental subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Objective deviation (deg)</th>
<th>Subjective deviation</th>
<th>Refraction</th>
<th>Acuity (Snellen)</th>
<th>Fixation (minarc)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>RE</td>
<td>LE</td>
<td>RE</td>
</tr>
<tr>
<td>NC</td>
<td>3</td>
<td>0</td>
<td>+5.25 sph</td>
<td>-5.25 sph</td>
<td>6/6</td>
</tr>
<tr>
<td>DD</td>
<td>17.5</td>
<td>11.5</td>
<td>+0.50 sph</td>
<td>-1.25 sph</td>
<td>6/6</td>
</tr>
<tr>
<td>JM</td>
<td>15</td>
<td>10</td>
<td>-3.00 sph</td>
<td>-3.00 sph</td>
<td>6/6</td>
</tr>
<tr>
<td>TN</td>
<td>5</td>
<td>2.5</td>
<td>-4.25 - 0.50 × 180</td>
<td>-2.50-0.25 × 85</td>
<td>6/6</td>
</tr>
<tr>
<td>AT</td>
<td>3</td>
<td>1.5</td>
<td>-4.25 sph</td>
<td>-4.50 sph</td>
<td>6/6</td>
</tr>
<tr>
<td>MT</td>
<td>8</td>
<td>5</td>
<td>+3.00-1.00 × 130</td>
<td>+1.75-1.00 × 50</td>
<td>6/6</td>
</tr>
</tbody>
</table>

RET = right esotropia, RXT = right exotropia, LET = left esotropia, nas = nasal, sup = superior.

The experimental amblyoscope findings were recorded during the evoked potential tests.
No. 3 RETINOTOPIC MAPPING AND ANOMALOUS CORRESPONDENCE / McCormack 561

Fig. 1. Scale drawing of targets (A) and electrode configuration (B). (A) 2° X 9° monocular stimulus fields were independently adjustable to any position along the horizontal meridian of the 35° X 27° binocularly viewed background. Each stimulus field contained a nonius line (upper-right eye) to guide the adjustment of stimulus fields onto corresponding points. Fixation point (X) and eye movement monitor calibration points (L, R) were seen by both eyes. Both stimulus fields normally were blank, but were replaced intermittently by a checkerboard field for one or the other eye (left eye shown here). (B) Six electrodes were fixed to the occipital scalp in all subjects. Occipital electrodes were referred to the right earlobe (R) while the left earlobe was grounded (G). 1, inion.

A Nicolet (Madison, WI) Med-80 system housed in an adjacent room controlled stimulus presentation and acquired, processed, and stored all data. Thus, the results of an experiment were not known to the experimenter until after the completion of an experiment. One hundred or 200 sweeps of the evoked potentials, strabismic deviation, and position of the deviated eye's target were averaged. The EEG, filtered from 0.5 to 100 Hz (Grass Instruments, Quincy, MA), was sampled at a rate of 630 Hz per electrode, and later digitally smoothed. The 400-msec evoked potential epochs from each eye were interleaved into separate memory bins.

Procedure

The experiment on corresponding points, performed on all subjects, entailed stimulation of the fovea of the straight eye and the point corresponding to it in the fellow eye. The experimenter centered the stimulus field seen by the straight eye on the fixation point. The subject then adjusted the position of the deviated eye's stimulus field until the left eye and
right eye nonius lines were aligned (ie, the subjective deviation was set to zero). The targets were then seen as fused and egocentrically “straight ahead.” In strabismic subjects, this procedure placed the straight eye’s target on the fovea and the deviated eye’s target onto the peripheral retina, while both targets fell upon the foveas in the normal subject. The subject continued to adjust the deviated eye’s stimulus field, as necessary, to keep the targets subjectively aligned throughout the corresponding points experiment. If the ARC shift hypothesis is correct, this procedure would ensure that both eye’s VEPs arose from fovea visual cortex, and that the eyes’ VEP topographies would be matched.

The bifoveal experiment, performed on subjects NC and TN, evaluated the ARC shift hypothesis through dichoptic stimulation of the anatomic fovea of each eye. The straight eye’s target was centered on the point of fixation, as in the corresponding points experiment. Throughout the bifoveal experiment the position of the deviated eye’s target was stabilized approximately on the fovea of the deviated eye, by manual feedback (by the experimenter) of the deviated eye position to the deviated eye’s stimulus field galvanometer. This procedure neutralized the angle of deviation, including slow drifts, to within the accuracy of the eye movement monitor.

VEPs from the deviated eye’s fovea were not recordable in the bifoveal experiment in subject NC. This lack of response was due apparently to suppression, since this subject reported that the deviated eye’s flashed checkerboard target was perceived only rarely when imaged on the fovea.

Srebro16 has shown that VEP laterality can resolve stimulus displacements of 30’ for stimuli near the fovea. Preliminary trials for the current study indicated that VEP topography is highly influenced by stimulus position when stimuli are near the fovea. Therefore, the position calibration of the eye-movement-monitoring system was checked several times during the bifoveal trial to ensure that the stimulus was centered on the deviated eye’s fovea. The slight degree of eccentric fixation found in subjects NC and TN was compensated for by the experimenter.

In the presence of an ARC shift, the bifoveal experiment would activate the foveal cortex through the straight eye and the peripheral cortex through the deviated eye, resulting in dissimilar VEP topographies.

**Results**

The right and left eye VEP topographies of normal subject SE were virtually the same in the corresponding points experiment (Fig. 2A). Despite the presence of considerable noise, the similar distribution of these VEPs over the scalp was evident, indicating the robustness of the VEP topography method. These VEPs had larger amplitudes over the right hemisphere, but this asymmetry was matched for the two eyes. This VEP topography match was a product of the similar retinotopic mapping of the two eyes in normal visual cortex.

To the right of these VEPs are shown the objective positions of the stimulus fields against the background (object space) and the perceived positions of those stimulus fields (visual space). Object and visual space were assumed to be equivalent for the normal subject.

The consequences of stimulating normally non-corresponding points on VEP topography is shown in Figure 2B. The stimulus was centered on the fovea in the right eye, and displaced 2.5° into the right visual field of the left eye. VEP topography was markedly different for right and left eyes, as shown by amplitude differences and polarity reversals up to 250 msec after stimulus onset. These changes are most evident across the occipital electrodes. Such amplitude and polarity changes defined a VEP topography shift and signified a movement of the VEP generator within the visual cortex. Comparable differences between right and left eye VEPs in strabismic subjects in the corresponding points experiment would refute the ARC shift hypothesis, since VEP topographies should be matched when corresponding points are stimulated.

Data from subject TN (Fig. 3) highlight the findings of these experiments on strabismic subjects. The corresponding points experiment (Fig. 3A) showed clear differences between the VEP topographies of the eyes for troughs and peaks ranging from 80 to 170 msec after stimulus onset, including polarity reversals over the left occipital and parietal scalp. Thus the VEP indicated that these responses arose from foveal and peripheral cortex of the straight and deviated eyes respectively, even though the stimuli which generated these responses were perceived to be straight ahead and centered on the fixation point through both eyes. On the other hand, VEP topographies were virtually identical in the bifoveal experiment (Fig. 3B), indicating that these VEPs arose from foveal visual cortex for both eyes, even though these stimuli elicited a subjective diplopia of approximately 2°. In both experiments, the parietal electrodes produced results similar to those obtained from the occipital electrodes, but with smaller amplitudes.

The results shown in Fig. 3 suggest that neurophysiologic correspondence was normal in TN’s visual cortex during binocular vision, despite ARC. A corollary to this suggestion is that the characteristic VEP
Fig. 2. Corresponding point (A) and noncorresponding point (B) stimulation. VEPs from normal subject SE demonstrate that stimuli alternately flashed onto corresponding points during binocular vision generate the same VEP topography in the two eyes (A), whereas stimuli alternately flashed onto noncorresponding points produce different VEP topographies in the two eyes (B). VEPs are shown to the left, and scale drawings of the central portion of the target configuration which generated those VEPs are shown to the right. Note that the arrangement of VEPs shown here is rotated 90° from the electrode placement shown in Figure 1. Object space: physical target configuration; visual space: target configuration as perceived by subject. Evoked potential calibration (VEPS) and object space target calibration (TARGETS) are shown above. One standard error = 1.6 µV.

Topographies derived from the deviated eye's fovea and pseudofovea should have remained fixed as subject TN reverted from binocular to monocular vision, even while subjective correspondence changed. In additional trials conducted on subject TN, the fovea and then pseudofovea of the normally deviated eye were stimulated during occlusion of the normally straight eye. Comparison of foveal VEP topographies in monocular and binocular vision (Fig. 4A) showed no change. Likewise, pseudofovea VEP topographies were the same in monocular and binocular vision (Fig. 4B). ARC appeared to have no effect on subject TN's VEP topographies.

The results of the corresponding points experiment for the other five subjects (Fig. 5) were qualitatively similar to those of subject TN. The distribution of VEP amplitudes across the occipital electrodes were distinctly different in the right and left eyes. Amplitude differences appeared up to 250 msec after stimulus onset in some subjects. The parietal electrode data are not shown since the parietal interocular differences were similar to differences at the occipital electrodes, as in subject TN (Fig. 3A). Figure 6 shows in graphic form the results of the corresponding points experiment on all seven subjects. Peak-to-trough VEP amplitude is plotted as a function of occipital electrode position for each eye. This measurement was made between the first major peak (80–100 msec) and the first major trough (120–150 msec). The obvious differences between the strabismic subjects' right and left eye peak-to-trough VEP topographies suggests that different cortical sites were activated by these subjectively corresponding stimuli.

In sum, VEP topography evidence from all six strabismic subjects showed that responses generated by stimuli placed on anomalously corresponding points arose from different cortical loci, whereas responses generated by stimuli placed on the foveas of each eye in one subject arose from the same cortical locus.

Discussion

The inability of ARC to induce a VEP topography shift indicates that there is no ARC shift in many
visual cortex cells. The extent to which this result can be generalized to all cases of ARC is not entirely clear. These subjects tended to have small to moderate squint angles and were selected to have little if any amblyopia. Anomalous retinal correspondence is more difficult to measure in amblyopes with significant acuity loss, and varies in incidence depending on many factors, such as angle of strabismus and the type of test used. However, there is no evidence that ARC, when detected, is fundamentally any different among the various types of strabismus. Consequently, the current results are expected to be valid for most, if not all, cases of ARC.

The application of these findings to specific brain sites is limited by current knowledge of the generators of VEPs. Jeffreys and Axford's findings on the probable origin of the C1 component of the pattern-onset VEP13 has been challenged, but also supported. Therefore, it is likely that my results apply to areas 17 (striate cortex) and 18 (parastriate cortex). The anatomic origins of the later components of pattern-onset VEPs are not yet clear, but the scalp topography of some of those later components in normals is strongly influenced by stimulus position on the retina (Fig. 2B). The absence of an ARC shift for those components (Figs. 3, 5) suggests that no cortical site contributing to the pattern-onset VEP undergoes an ARC shift. However, it is possible that an ARC shift could occur at sites beyond the visual cortex or in the brain stem but not appear in the VEP. It is possible also that subpopulations of visual cortex cells undergo retinotopic remapping due to ARC, but do not reveal themselves in the VEP either because they are electrophysiologically silent or because they are too
Fig. 4. Monocular versus binocular VEPs are compared for anatomic fovea stimulation of the deviated eye (A) and for pseudofovea stimulation of the deviated eye (B) in strabismic subject TN. There is no change of VEP topography at either retinal site as vision is changed from binocularity to monocularity, despite the presence of perceived direction changes. The binocular vision VEPs of the deviated eye are taken from Figure 3. The monocular VEPs from the fovea and pseudofovea were recorded in separate experiments during occlusion of the straight eye. The visual field drawings show the deviated left eye’s target position within the objective visual field, and the visual space drawing compares the different perceived loci of the stimuli in monocular and binocular vision. One standard error = 0.8 μV.

few to make a significant impact on the VEP. Both Nelson\textsuperscript{19} and Pickwell\textsuperscript{20} have proposed physiologic hypotheses involving defects in subpopulations of cells that could account for ARC, but physiologic data in support of these hypotheses are lacking. Pickwell suggested that suppressed Y-cell activity from the deviated eye could account for ARC, based on the presumption that Y-cell activity is important for normal spatial localization.\textsuperscript{20} If Pickwell’s hypothesis were correct, the deviated eyes in the current study should have produced significantly reduced amplitudes and increased implicit times due to the absence of response from an entire class of cortical cells. However, the current data did not behave as predicted by Pickwell’s argument (Figs. 3, 5). Therefore, Pickwell’s hypothesis, as related to visual cortex function, is not consistent with the results of the current study.

Nelson\textsuperscript{19} proposed that a shift of mean disparity detector activity from the foveas to a convergent disparity (exotropes) or divergent disparity (esotropes) produces ARC. Since the great majority of visual cortex cells are monocular in animal models of squint,\textsuperscript{21} not many cells would participate in Nelson’s proposed disparity shift. Consequently, this disparity shift might not impact significantly on the VEP. Reconciling Nelson’s hypothesis with my results requires acceptance of the argument that a small number of disparity detector cells (not significantly contributing to the VEP) controlled the deviated eye’s visual direction perception during binocular vision, while the large number of cells which produced these VEPs made no contribution to visual direction perception. Although the above argument may be viewed as weak, reports of sizable VEPs recorded from patients cortically blinded by organic damage to visual cortex\textsuperscript{19,22,23} indicates that generation of VEPs by masses of cells does not prove the presence of perception. Since this dissociation of VEP and per-
The results of the corresponding points experiment on the other five strabismic subjects are similar to those of subject TN, showing different VEP topographies from the straight and deviated eyes. Only the occipital electrode data are shown. These data are comparable to the occipital electrode data of Figure 3A.

These VEP results do not seem to be in accord with Campos and Chiesi's report\textsuperscript{12} that they identified ARC in the human VEP. Their method was based on VEP measurement of binocular summation. While their methods revealed binocular enhancement (a larger binocular VEP than monocular VEP), there is some doubt as to whether their methods conclusively demonstrated binocular summation (a true binocular interaction) on anomalously corresponding points. Their stimulus field was large enough to encompass the foveas of both eyes of their strabismic subjects during binocular vision, in addition to the anomalously corresponding points. Thus, binocular VEP enhancement may have resulted from bifoveal interaction rather than from interaction on anomalously corresponding points. Apkarian et al\textsuperscript{24} found binocular facilitation in the VEP (binocular response greater than the sum of monocular responses) when stimuli were placed on the foveas of each eye in squint; this result provides strong evidence for true binocular interaction. Such facilitation has not been demonstrated with stimuli placed only on anomalously corresponding points. Also, binocular VEP enhancement may arise simply because the stimulus, imaged onto different retinal regions in the two eyes, activates physiologically separate cortical loci whose electrical responses sum at the recording electrode.\textsuperscript{25} Therefore, the binocular VEP amplitude enhancement Campos and Chiesi observed may not correlate to physiological summation on anomalously corresponding points.

While my results rule out gross retinotopic remapping in the visual cortex due to ARC, they do not apply to any retinotopic remappings that may be caused by amblyopia, since amblyopes were excluded from this subject population. Bedell and Flom\textsuperscript{26} measured significant spatial distortion in the amblyopic eye of squint amblyopes, and attributed the visual distortion to distorted retinotopic mapping in the visual cortex. They also found small magnitudes of this perceptual distortion (in minutes of arc) in squinters who did not have clinical amblyopia. If this
type of remapping were present in the subjects tested in the current study, it would have evaded detection since my methods did not have sufficient resolution to detect VEP topography shifts related to target displacements of a few minutes of arc. Other VEP experimental paradigms might successfully answer the question of whether cortical retinotopic remapping related to spatial distortion occurs in squint amblyopia.

Eccentric fixation is another characteristic of squint amblyopia for which the question of cortical remapping should be considered. Srebro used the VEP to test for eccentric fixation in squint amblyopia. His results imply that during monocular vision, the fovea of the amblyopic eye projects to foveal visual cortex as does the fovea of the normal eye. The perceptual significance of this result is that the eccentrically fixating retinal point, associated with the retinomotor percept of “straight ahead” in monocular vision, must be physiologically connected to a locus in the visual cortex normally devoted to peripheral vision. Therefore, the anomalous sense of “straight ahead” in eccentric fixation, like ARC, does not appear as a remapping in the visual cortex.

The disagreement of the ARC shift hypothesis with my results suggests that ARC may not take place in
visual cortex areas 17 and 18, or that if it does, it must not be encoded in the retinotopic mapping of those areas. The search for the physiologic basis of ARC probably should be focused on other sites in the brain.

Key words: strabismus, anomalous retinal correspondence, visual cortex, visual evoked potentials, retinotopic mapping

Acknowledgments

The author thanks Dr. Eli Peli, Dr. Samuel Sokol, and Dr. Frank Thorn for their helpful comments and suggestions on the manuscript and Dr. Indra Mohindra for the referral of several subjects.

References