Misrouting of the Optic Nerves in Albinism: Estimation of the Extent with Visual Evoked Potentials

Michael B. Hoffmann,[1] *Birgit Lorenz,*[2] *Antony B. Morland,*[3] *and Linda C. Schmidtborn*[1,4]

Purpose. In human albinism a part of the temporal retina projects abnormally to the contralateral hemisphere. An objective VEP procedure to quantify the extent of the abnormality was devised.

Methods. Monocular VEPs were recorded in 16 subjects with albinism and in 16 controls from occipital electrodes to pattern-onset stimulation in 1 of 10 adjacent rectangular apertures along the horizontal meridian covering a total of ±27°. For each eye interhemispheric difference potentials were calculated and correlated with each other to assess the lateralization of the responses: positive and negative correlations indicate lateralization on same or opposing hemispheres, respectively. Different stimulus conditions were compared to assess the sensitivity and specificity of the procedure for the detection of the misrouting of visual projections in albinism.

Results. Locations that were affected by the projection abnormality were detected with a specificity of 100% and an average sensitivity of 97%. In the 16 subjects with albinism tested, the abnormal projection was confined to the central retina and varied in extent between subjects (2°-15°; median, 8°). The extent did not appear to be correlated with horizontal nystagmus amplitude or visual acuity.

Conclusions. Because of the great interindividual variability of the projection abnormality, studies of the contribution of the abnormally projecting retina to visual perception must be preceded by the localization of the abnormality. This VEP procedure allowed the authors to identify, with high sensitivity and specificity, visual field locations that are affected by the projection abnormality. (*Invest Ophthalmol Vis Sci.* 2005;46:3892–3898) DOI:10.1167/iovs.05-0491

In humans, the nasal retina projects to the contralateral hemisphere, whereas the temporal retina projects ipsilaterally. Consequently, the line of decussation that divides crossed from uncrossed fibers normally coincides with the vertical meridian through the fovea. This normal projection of visual fibers from the retina is severely disrupted in albinism, where the line of decussation is shifted into the temporal retina. As a consequence, a great number of fibers from the temporal retina cross the midline at the optic chiasm and project contralaterally.[1–7] Because of this projection abnormality, the primary visual cortex receives—in addition to the normal input from the contralateral hemifield—abnormal input from the ipsilateral hemifield. This abnormal visual field representation makes albinism a promising model to examine cortical self-organization in humans, and it is important to understand how and to what extent visual function of the abnormal cortical visual field representation is preserved. Before these questions can be addressed, it is vital to determine whether a distinct visual field location is actually affected by the projection abnormality. This is particularly relevant because some early VEP reports on albinism indicate that only part of the temporal retina is misrouted.[8] Moreover, they indicate the possibility of a great interindividual variability of the extent by which the line of decussation is shifted to the temporal retina.[9]

The refinement of VEP paradigms to detect the misrouting of visual projections in combination with objective analysis procedures has made the VEP a valuable tool to assist the detection of albinism in clinical routine. Apkarian et al.[10] compared the interhemispheric activation differences obtained from occipital derivations for left and right eye stimulation after simultaneous central stimulation in both hemifields. They reported a sensitivity and a specificity of 100% for this procedure in the detection of the misrouting of the optic nerves associated with albinism. This paradigm, which we will refer to as the standard albino-VEP paradigm, is based on the rationale that in albinism, the polarities of the interhemispheric difference VEPs obtained for left and right eye stimulation are inverted because each eye predominantly projects to the contralateral hemisphere. In controls, however, the polarities of the respective interhemispheric difference VEPs are not inverted because both eyes project to both hemispheres. Soong et al.[11] recently supplemented this approach with a simple objective analysis. They showed that, as a result of the polarity inversion, the interhemispheric activation differences for the two stimulation conditions (left and right eye) are likely to be negatively correlated in albinism. In control subjects—that is, in the absence of such a polarity inversion—the differences are likely to be positively correlated. In their study, Soong et al.[11] detected misrouting in subjects with albinism with a similarly high accuracy for the Apkarian et al.[10] approach and the correlation approach.

These procedures allow one to detect the misrouting of the optic nerves objectively with great sensitivity and specificity, but they do not allow one to differentiate between parts of the visual field that are misrepresented and parts that are not. We adapted these procedures to detect the projection abnormality in a spatially resolved manner, evaluated the specificity and sensitivity of this approach, and determined the interocular and intersubject variability of the extent of misrouting. Further, we tested whether the intersubject variability was related to visual function and to the VEP asymmetry determined with the standard albino-VEP paradigm for the detection of misrouted optic nerves.

Methods

Within the same recording session, we conducted two VEP experiments in subjects with albinism and in control subjects. In experiment

From the [1]Visual Processing Laboratory, Universitäts-Augenklinik, Magdeburg, Germany; [4]Sektion für funktionelle Sehforschung, Universitäts-Augenklinik, Freiburg, Germany; [2]Abteilung fur Kinderophthalmologie, Strabismologie und Ophthalmogenetik, Klinikum der Universität, Regensburg, Germany; and [3]Department of Psychology Royal Holloway, University of London, Egham, Surrey, United Kingdom.

Supported by German Research Council Grant HO-2002/3–1.

Submitted for publication April 21, 2005; revised May 27, 2005; accepted July 25, 2005.

Disclosure: **M.B. Hoffmann**, None; **B. Lorenz**, None; **A.B. Morland**, None; **L.C. Schmidtborn**, None

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: Michael B. Hoffmann, Universitäts-Augenklinik, Visual Processing Laboratory, Leipziger Strasse 44, 39120 Magdeburg, Germany; michael.hoffmann@medizin.uni-magdeburg.de.

Investigative Ophthalmology & Visual Science, October 2005, Vol. 46, No. 10

1, we recorded VEPs to stimulation in the left or right hemifield and thus determined the extent of the abnormal representation of the visual field along the horizontal meridian. In experiment 2, we recorded VEPs to simultaneous stimulation in both hemifields and thus assessed whether the standard albino-VEP paradigm[10,11] would reveal abnormal or normal routing in subjects with and without albinism, respectively. Apart from stimulus layout and sequence, both experiments were performed under identical conditions.

Subjects

Sixteen subjects with albinism (age range, 22–71 years; 12 men, 4 women) and 16 age- (within 2 years) and sex-matched controls with normal visual acuity (if necessary, with refractive correction) gave their informed written consent before the study. The procedures followed the tenets of the Declaration of Helsinki,[12] and the protocol was approved by the ethics committee of the University of Freiburg in Germany. Patients with albinism were included after the clinical diagnosis of albinism. We determined monocular visual acuity,[13] binocular visual function (Titmus stereo test, TNO test for stereoscopic vision), and horizontal nystagmus amplitude (with electro-oculography) in these patients.

Visual Stimulation

Stimuli were generated on a personal computer (Power Macintosh G4; Apple, Cupertino, CA) with a program based on game sprockets (Apple)[14] and were presented on a cathode-ray tube with a frame rate of 75 Hz. Left and right eyes were stimulated monocularly in separate blocks at a viewing distance of 30 cm. Visual stimuli (black-and-white checkerboard patterns; 98% contrast; mean luminance, 22 cd/m^2) were presented in pattern onset-offset mode (40 ms on, 440 ms off) because this has been shown to be an effective stimulus in patients with nystagmus and in those with albinism.[15,16] In experiment 1, stimuli were presented in a randomized order in 1 of 10 adjacent rectangular apertures along the horizontal meridian (Fig. 1). The randomized presentation order ensured that the participants could not systematically divert fixation from the fixation target to look at the presented stimulus patterns. The sizes of the square checks and the horizontal extents of the stimuli increased with increasing eccentricity (horizontal extent in left or right hemifield (check size): 0° to 2.5° (1.2°), 2.5° to 6° (1.2°), 6° to 11.5° (1.4°), 11.5° to 17° (1.8°), 17° to 27° (2.5°); vertical extent: ±12°). In experiment 2, both hemifields were stimulated simultaneously either with a uniform checkerboard (1.2° check size; check size with high efficiency in the detection of albinism[10]) or with a checkerboard whose check sizes were identical to those in experiment 1. For the latter, the pattern consequently consisted of different check sizes, depending on eccentricity along the horizontal meridian (a composite of the stimulus stripes depicted in Fig. 1). Both patterns were presented in one of three apertures (horizontal and vertical extent, respectively: ±27° and ±27°; ±27° and ±12°; ±12° and ±12°), resulting in a total of six stimuli. These six stimuli thus differed in the selectiveness with which they stimulated the central visual field. In experiments 1 and 2, subjects were instructed to look at the center of a red fixation cross that spanned the entire display.

Electrophysiologic Recordings

VEP Recordings. Electrodes were placed and labeled according to the international 10–20 System.[17] Potentials were recorded from the four scalp electrodes (O_1, O_2, PO_7, and PO_8) referenced to F_z. The ground electrode was attached to the right wrist. Signals were amplified, filtered (first-order bandpass, 0.3–70 Hz; Toennies Physiologic Amplifier, Höchberg, Germany), and digitized to a resolution of 12 bits at a sampling frequency of 1 kHz on a personal computer (Macintosh 7100; Apple). Using LabView (National Instruments, Austin, TX), signals were "streamed to disk" and averaged on-line so that recordings could be monitored.

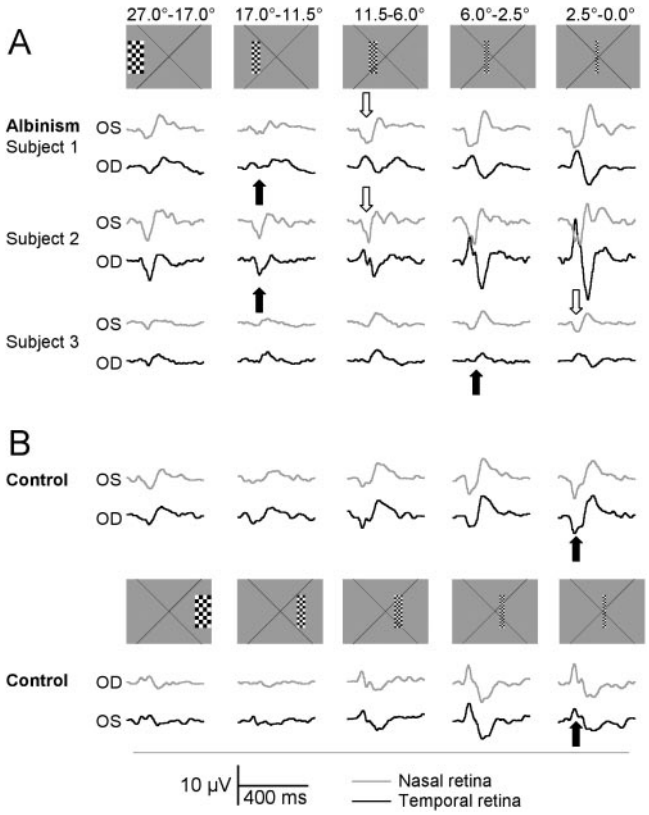

FIGURE 1. VEP difference traces indicate the interhemispheric activation differences for stimulation in the nasal (*gray*) and temporal retinas (*black*) in three subjects with albinism (**A**; stimulation in the left visual hemifield) and in one control (**B**; both hemifields). Opposite polarities for nasal and temporal stimulation indicate an abnormal representation (extent is indicated by *open arrows*), and similar polarities indicate a normal representation (extent is indicated by *filled arrows*) of the respective visual field location. In albinism, the abnormality affected the central visual field and differed in extent between subjects. In the control, the polarity did not invert for right (OD) and left (OS) eye stimulation at the same visual field locations but did invert for stimulation at corresponding locations in opposing hemifields.

EOG Recordings. Spontaneous nystagmus was evident in most subjects with albinism. We recorded the horizontal electro-oculogram (EOG) bitemporally to assess the amplitude of the nystagmus during the VEP recordings and the vertical EOG of the left eye for blink detection. EOGs were amplified, filtered (first-order bandpass, 0.3–70 Hz; Toennies Physiologic Amplifier), and digitized at a sampling rate of 1 kHz. Horizontal EOGs were calibrated just before the beginning and at the end of each VEP recording.

Procedure

An entire recording session lasted approximately 3 hours, including preparation and breaks. Stimuli for experiments 1 and 2 were presented monocularly in interleaved blocks. Ten (experiment 1 [E1]) or six stimuli (experiment 2 [E2]) were repetitively presented in randomized order in the same block to either the left eye (OS) or the right eye (OD), 50 (E1) or 62 (E2) repetitions per condition in each block. The succession of blocks was counterbalanced (a-b-b-a scheme: $E1_{OS}$, $E1_{OS}$, $E2_{OS}$, $E1_{OD}$, $E1_{OD}$, $E2_{OD}$, $E2_{OD}$, $E1_{OD}$, $E1_{OD}$, $E2_{OS}$, $E1_{OS}$, $E1_{OS}$). A total of 200 or 124 stimuli per condition and eye were presented for E1 and E2, respectively.

Data Analysis

VEP Analysis. Trials were analyzed off-line with Igor Pro (Wavemetrics, Lake Oswego, OR). Trials with blinks detected with a thresh-

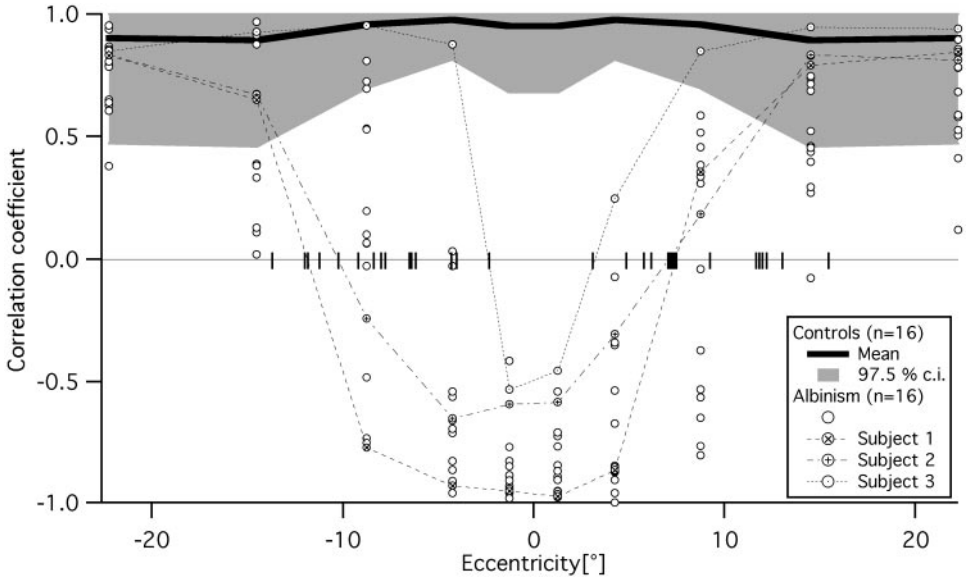

FIGURE 2. Dependence of the visual field representation on eccentricity along the horizontal meridian for 16 subjects with albinism and 16 controls. Positive correlation of left and right eye responses indicates a normal representation, and negative correlation indicates an abnormal representation. *Open symbols* indicate values for subjects with albinism for each eccentricity stimulated. *Vertical lines* along the zero-line indicate the eccentricity beyond which a normal visual field representation prevailed. Subjects 1 to 3 are the examples given in Figure 1. The *hatched gray* area indicates the 97.5% confidence interval (c.i.) for the control population (mean and c.i. were calculated with *z*-transformed data and were transformed back for the illustration). In albinism, the projection abnormality affects the central visual field and extends for a variable extent into the periphery.

old criterion of 100 μV applied to the vertical EOG and the EEG recordings were discarded. Sweeps were pooled according to stimulus conditions and were digitally filtered (0–40 Hz) before averaging. VEPs from neighboring electrodes over the same hemisphere were averaged (O_1 and PO_7; O_2 and PO_8) to increase the signal-to-noise ratio. Differences of the averaged VEPs recorded over opposing hemispheres were calculated to assess the lateralization of the responses. Difference traces obtained for each eye were correlated with each other to obtain Pearson correlation coefficient (r; range, -1 to 1). Thus normal and abnormal projections of the optic nerves can be distinguished. Positively correlated traces indicate that both eyes project to the same cortical regions, and negatively correlated traces indicate that both eyes project to opposing hemispheres.[11] It should be noted that this is a more objective approach than a single peak analysis, which allows one to deal with small signal amplitudes. We adjusted the time window used by Soong et al.[11] (from 0 to 200 ms after stimulus onset) for the correlation of the traces to cover most of the response in the difference VEP; thus, the window spanned 50 to 250 ms after stimulus onset.

For comparison, we also conducted conventional analysis of the individual difference VEPs and assessed the peak at approximately 100 ms after stimulus onset. We compared the peak polarity of the difference VEPs of the left eye and the right eye obtained after stimulation at the same stimulus location. The same polarity indicated normal projection, whereas the opposite polarity indicated abnormal projection. For this analysis, baseline was defined as the mean value of the averaged trace from 100 ms before to 70 ms after stimulus onset and was used as zero reference for peak measurements.

EOG Analysis. EOG traces were analyzed off-line with Igor Pro (Wavemetrics). Recordings were digitally filtered (0–40 Hz) and reintegrated to compensate the high-pass filtering (cut-off frequency, 0.3 Hz). Amplitude of the horizontal nystagmus during the VEP recordings was determined for each eye from the EOG traces recorded during the stimulation of the respective eye.

Statistical Analysis

Because Pearson's correlation coefficient (r) is not normally distributed, we converted r to a normally distributed variable using Fisher z-transformation for averaging and for determination of the confidence intervals. We back-transformed the obtained values for the illustrations, if not otherwise stated. Multiple regression analysis was applied to assess the correlation of the extent of misrouting determined in experiments 1 and 2. Regressions were subsequently tested for significance with Student t-test, and the obtained values were α-adjusted for multiple testing using the Bonferroni correction.

RESULTS

Determining the Shift of the Line of Decussation

Examples of the VEP traces for subjects with albinism with differing degrees of misrouting and for a control subject are depicted in Figure 1A and 1B, respectively. In the three subjects with albinism, a reversal of the polarity of the interhemispheric activation difference for left compared with right eye stimulation can be observed in the visual field center. This polarity reversal indicates the misrouting of the optic nerves, specifically of the fibers from the central temporal retina. In the periphery there is an absence of such a polarity reversal, indicating that with increasing eccentricity the projection of the optic nerve reverts to the normal pattern (Fig. 1A). For the control subject, an absence of a polarity reversal is evident for all eccentricities, demonstrating the normal projection pattern expected in the control. Although the normal projection pattern does not lead to a polarity reversal for left compared with right *eye* stimulation, it does lead to a polarity reversal for stimulation in the left compared with the right *hemifield* because opposing hemifields are represented on opposing hemispheres (Fig. 1B).

Quantification of the Shift of the Line of Decussation

The polarity of the interhemispheric activation differences for different stimulus conditions can be quantified objectively by correlating the differences obtained for stimulation of the left eye and the right eye with each other.[11] The absence of a polarity reversal (i.e., normal projection) causes the activation differences to be positively correlated, whereas the presence of a polarity reversal (i.e., abnormal projection) causes them to be negatively correlated. In Figure 2, the correlation coefficients for 16 subjects with albinism are depicted as a function of stimulus eccentricity. The correspondence of correlation coefficients and raw traces can be appreciated by comparing the difference traces of the examples in Figure 1 with their respective correlation coefficients in Figure 2. For the subject with a restriction of the polarity reversal to the visual field center, negative correlation coefficients were only obtained in the center. For the other two subjects, negative correlations could be obtained for more peripheral stimuli. The eccentricity beyond which the normal projection prevails can be deter-

mined as the eccentricity at which the correlation coefficient obtains a value of zero (i.e., as the zero crossing of the function correlation coefficient versus eccentricity). In Figure 2, these zero crossings are indicated for each of the 16 subjects with albinism by vertical lines at zero correlation. The distribution of the data is detailed in the Interocular and Interindividual Variability of the Shift of the Line of Decussation section.

For comparison, we also determined the projection abnormality with a single peak analysis of the difference VEPs, as detailed in the Methods section. We did not expect both approaches to yield exactly the same results because single peak analysis is particularly error prone in the absence of pronounced signals. Still we report a remarkably high correlation of the results obtained with these two techniques ($P < 0.00001$; $r = 0.73$).

Specificity and Sensitivity of the Correlation-Based Detection Procedure

The accuracy of the detection procedure was assessed by determining its specificity from control data and its sensitivity both from control data and from subjects with albinism. The specificity of the detection of the misrouting of the optic nerves is indicated in Figure 2, where the mean correlation coefficients ± 2 SD (97.5% confidence interval) of the 16 control subjects are depicted. It is evident that a correlation coefficient threshold of 0 allows one to detect the misrouting with a *specificity* of 100% (i.e., without false alarms).[2] To assess the *sensitivity* of the detection procedure, one has to determine the proportion of negative correlation coefficients obtained for a pair of cortical responses that are *known* to be localized on opposite hemispheres. Such a measure can be derived from the control data. In controls, responses to stimuli in opposing visual hemifields are lateralized on opposing hemispheres. Thus, sensitivity can be estimated for each stimulated eccentricity by correlating the difference VEPs obtained for stimulation in the left and the right hemifields at the same absolute eccentricity. We determined the proportion of negative correlation coefficients as a measure for the sensitivity from the control data for the respective eccentricities (0°-2.5°, 2.5°-6.0°, 6.0°-11.5°, 11.5°-17.0°, and 17.0°-27.0°): 96.5%, 100%, 100%, 91%, and 88%. The decrease of sensitivity toward the periphery is likely to be associated with a decrease of the signal-to-noise ratio of the signals in the periphery. Further, interhemispheric asymmetries of cortical morphology are likely to contribute to a reduction of the sensitivities. While the above sensitivity estimate is derived from control data, a similar approach can be taken directly with the data from the subjects with albinism. In albinism, the nasal retinas of both eyes follow the normal projection pattern and are represented on opposing hemispheres. A correlation of the interhemispheric activation differences for stimulation at the same eccentricities of the nasal retina of both eyes is, therefore, expected to yield negative correlation coefficients. Indeed, we obtained, in all subjects with albinism and for the 5 visual field positions tested, negative correlation coefficients (i.e., 100% sensitivity). These results underscore the high sensitivity of our approach and indicate that interocular differences within a subject do not corrupt the correlation analysis. Taking the results for controls and subjects with albinism together, the data indicate the following sensitivities for the respective eccentricities (0°-2.5°, 2.5°-6.0°, 6.0°-11.5°, 11.5°-17.0°, and 17.0°-27.0°): 98%, 100%, 100%, 94%, and 92% (average sensitivity, 97%).

Interocular and Interindividual Variability of the Shift of the Line of Decussation

To assess the interocular variability of the shift of the line of decussation within a subject, we calculated the coefficient of variation (SD/mean) for the measured shifts of both eyes and obtained 23% ± 13% as the average coefficient of variation for the 16 subjects with albinism (for comparison, the coefficient of variation across all subjects with albinism was 38%). In one of these subjects, we were able to detect pronounced monocular eccentric fixation in association with strabismus and obtained a coefficient of variation as high as 43%, which implies that eccentric fixation might underlie the residual interocular variability of the extent of misrouting observed in our data. To reduce the influence of such eccentric fixation on further analysis, we used the position of the line of decussation as determined for the habitually fixating eye for further evaluation of the data set. Obtained values ranged from 2.4° to 15.4°, with a median of 8°. In 2 (13%) subjects, the line of decussation shifted by <5° into the temporal retina; in 9 (56%) subjects, it shifted by 5° to 10°; in 5 (31%) subjects, it shifted by 10° to 15.5°; in no subjects did it shift by >15.5°.

Most of our subjects were identified to have OCA1 albinism. For these 8 subjects, the shift of the line of decussation ranged from 5.9° to 12.1° (median, 7.2°). In none of these subjects did the shift fall short of 5°, indicating the possibility that genotype might influence the magnitude by which the line of decussation shifted into the temporal retina. For one of the two subjects identified as having ocular albinism, the shift did not exceed 5° (4.9°), whereas it was 13° for the other subject.

Relation between the Shift of the Line of Decussation and the Detection of Misrouting in the Standard Albino-VEP Paradigm

The same subjects in whom we quantified the shift of the line of decussation (experiment 1) were also assessed with the standard albino-VEP paradigm (experiment 2). In experiment 2, we compared the interhemispheric activation difference obtained for right and left eyes during *simultaneous* stimulation in both hemifields applying the same correlation procedure used in experiment 1. We report that in all subjects with albinism, the difference traces obtained for right and left eye stimulation were negatively correlated (indicative of misrouted pathways), whereas the difference traces were positively correlated in all control subjects (indicative of normal pathways). These results confirm previous findings obtained with flash VEPs in children[11] and highlight their relevance for pattern-onset responses in adults. The effect was robust across the different stimulus patterns and apertures used (Fig. 3A). In subjects with albinism, the correlation coefficients were slightly, but significantly, more negative for the largest aperture than for the other two apertures used (r: −0.90 vs −0.86; $P = 0.002$; repeated-measures ANOVA).

These results prompted us to test whether the correlation coefficients obtained with the standard albino-VEP paradigm (experiment 2) already indicated the size of the shift of the line of decussation determined in experiment 1. We tested for such a correlation between the results of experiments 1 and 2 by using multiple regression analysis (Fig. 3B) and obtained a significant negative correlation of the z-transformed correlations for the standard albino-VEP paradigm and the size of the shift of the line of decussation ($P = 0.028$). The relationship was greatest for the unscaled horizontal stripe (α-adjusted, $P = 0.012$; $r = -0.524$) and was weakest for the scaled full-field stimulus (P = n.s.; $r = -0.316$). Hence, there was a correlation between the results of experiment 1 and those of experiment 2, but this correlation was not strong enough to predict, on a case-by-case basis, the result of experiment 1 from the results of experiment 2.

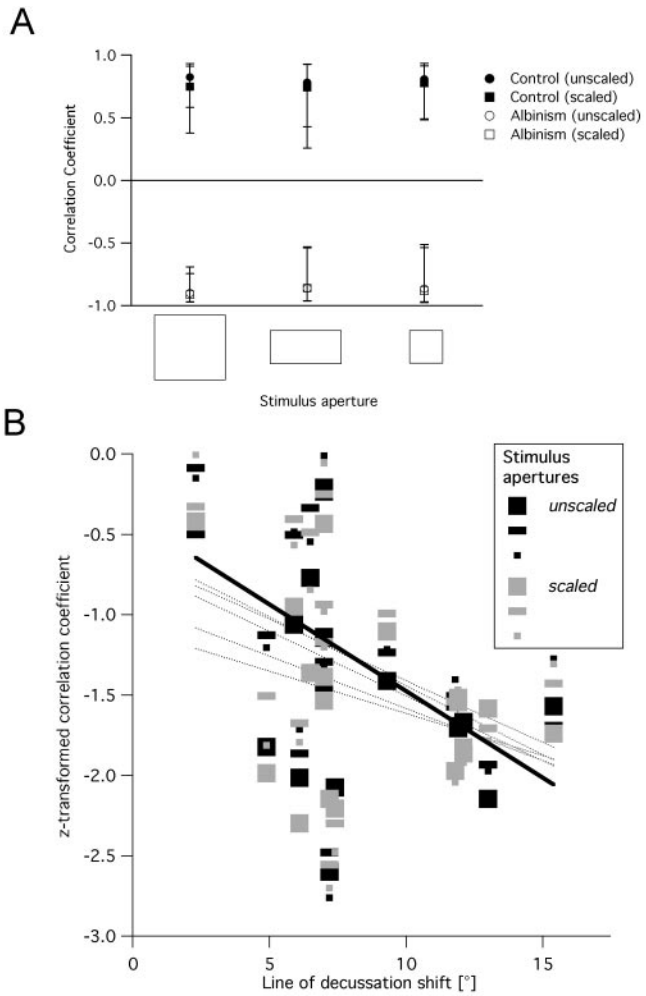

FIGURE 3. (**A**) Correlations of left and right eye responses obtained for simultaneous stimulation in both hemifields (standard albino-VEP paradigm) within three apertures (center and periphery, horizontal stripe, and center; detailed in the Visual Stimulation section) and two test patterns (unscaled, or uniform checkerboard pattern; scaled, as in experiment 1) for 16 subjects and 16 controls (mean ± 1 SD; data were *z*-transformed before averaging and were transformed back for the illustration). Correlations did not differ across stimulus conditions, but between subject groups, they were positive for controls and negative for albinism. (**B**) The *z*-transformed correlation coefficients obtained with the standard albino-VEP paradigm versus the shift of the line of decussation, as determined in experiment 1 (16 subjects with albinism; 6 different stimulus conditions for the standard albino-VEP paradigm). The strongest correlation was obtained for the unscaled horizontal stripe condition (*black* regression line; regression lines for the other conditions are *dotted*).

Relation between the Shift of the Line of Decussation and Visual Function

Next, we tested for a relationship between the shift of the line of decussation and visual function. We determined horizontal nystagmus amplitude, visual acuity, and binocular vision in the subjects with albinism. As evident from Figure 4, there was no significant correlation between the extent of misrouting and the horizontal nystagmus amplitude ($r = -0.36$) or the logarithmic visual acuity ($r = -0.09$). For the Titmus stereo test, 6 of 16 subjects tested positive (number of subjects positive for Titmus fly: 6; for circles of 800″ and 400″, 4 and 0, respectively), but, because this test contains monocular cues,[18] stereovision was also tested with the TNO test for stereoscopic vision, which failed to reveal stereovision in any of the 16 patients. The outcome of the Titmus stereo test was not related to the extent by which the line of decussation was shifted.

DISCUSSION

Correlation-based interocular comparison of the interhemispheric VEP differences allows detection of the projection abnormality typical for albinism in a spatially resolved manner with 100% specificity and an average sensitivity of 97%. We report a projection abnormality predominantly in the central retina and a high degree of interindividual variability of 13° (i.e., a range of 2° to 15°).

Correlation-Based Interocular Comparison of the Interhemispheric Activation Difference

The detection of albinism with the interocular comparison of interhemispheric VEP differences, as initially introduced by Apkarian et al.,[10] requires a single peak analysis and is, therefore, error prone in the absence of pronounced signals. An alternative, more objective analysis to assess whether difference traces for left and right eye stimulation invert polarity is the calculation of Pearson's correlation coefficient, which is positive in the absence and negative in the presence of the projection abnormality typical for albinism. Song et al.[11] compared the technique of Apkarian et al.[10] with the correlation approach and reported both approaches to have similarly high accuracy for detecting albinism, thus validating the correlation approach. In the present study, we used the more objective analysis with Pearson's correlation coefficient primarily because we expected signals to be small, especially for stimulation of the peripheral retina.

There is one potential caveat to the detection of projection abnormalities with a correlation-based approach. Interocular latency differences, such as attributed to amblyopia, might shift the peaks of the difference VEPs obtained for the two eyes with respect to each other and might thus lead to incorrect assessment of the projection pattern. We tested directly whether the correlation results were corrupted by interocular latency differences. Because the nasal retinas of the left and right eyes are represented on opposing hemispheres, the interocular correlation coefficients of the difference VEPs to stimulation of the nasal retinas are expected to be negative (see the Specificity and Sensitivity of the Correlation-based Detec-

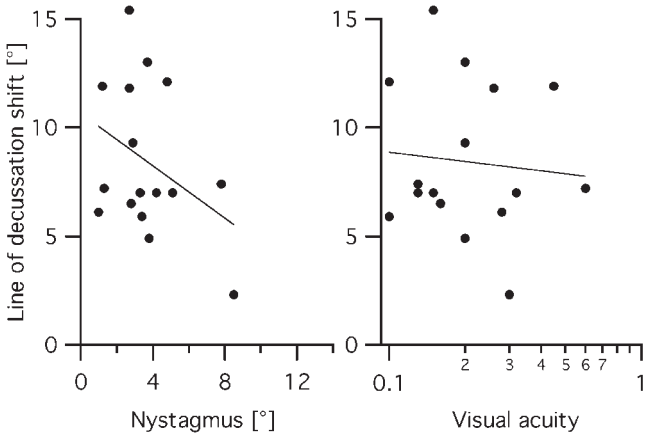

FIGURE 4. Shift of the line of decussation as a function of nystagmus amplitude and visual acuity for 16 subjects with albinism. There was no significant correlation between the magnitude of the shift of the line of decussation and the horizontal nystagmus amplitude (*left panel*) and visual acuity (*right panel*).

tion Procedure section). This held for all our subjects with albinism, thus underscoring the accuracy of the approach. In addition, a quantitative evaluation showed that interocular latency differences were unlikely to have corrupted the correlation-based approach: given that a difference trace consisted of a succession of deflections with the negative and positive peaks separated by approximately 60 ms (see Fig. 1), interocular latency differences would have to have exceeded 30 ms for the sign of the correlation coefficient to have been changed. The interocular VEP delays associated with amblyopia are typically smaller[19,20] and are confined to the central 2° of the visual field.[21]

Extent of the Projection Abnormality

Great interindividual variability of the abnormal cortical response lateralization is typical for studies based on the standard albino paradigm.[6,22] Although these studies do not allow differentiation between representation abnormalities of circumscribed visual field locations, they motivate the hypothesis that it might be the extent of the affected visual field that varies between subjects. Indeed, a variability in the affected visual field has previously been suggested.[9] This early VEP study did not benefit from the use of interocular comparison, the objectivity of a correlation-based analysis, and the avoidance of systematic fixation deviation, which might contribute to the fact that abnormalities greater than 20° were reported. Here we integrated these features in a VEP paradigm and report a projection abnormality that varies between subjects within a range of 2° to 15°. This range is supported by a previous functional magnetic resonance imaging (fMRI)–based retinotopic mapping study that reported abnormalities between 6° and 14°.[23] Cross-validation of both approaches is under way, and preliminary data indicate a correspondence between the results obtained with VEP and fMRI. For determining the horizontal extent of the projection abnormality, the VEP paradigm might be preferable to fMRI-based retinotopic mapping because it is less demanding of the cooperation of the subjects and of the analysis procedures involved.[24,25]

Intersubject Variability

Clearly, a larger sample is needed to incontrovertibly assess the cause and consequences of the variability we observed in the extent to which the line of decussation is shifted into the temporal retina in albinism. At present, the data indicate several factors. First, the shift of the line of decussation was not related to the amplitude of the spontaneous nystagmus of these patients, which suggests that horizontal nystagmus is not a major confound in our measurements. Second, it would be of great interest to understand whether the extent of the projection abnormality is related to visual function. Thus far, we tested whether the subject's visual acuity was related to the extent of the abnormality and failed to discern a relationship. Third, because none of our subjects showed evidence of global stereopsis[26] in random dot paradigms, it was not possible to test the hypothesis that residual stereopsis in albinism is mediated by residual normal projection and, therefore, is associated with a particularly small extent of the projection abnormality. For the standard albino paradigm, a correlation between projection abnormality and clinical features of albinism has previously been reported in a study with 40 subjects.[22] It might, therefore, be promising to increase the sample size to examine a potential correlation between clinical features of albinism and the extent of the shift of the line of decussation.

As expected, abnormal lateralization produced more negative correlation coefficients in the standard albino-VEP paradigm with increasing extent of the shift of the line of decussation along the horizontal meridian. However, the differences in the correlation coefficients obtained with the standard albino paradigm for different stimulus apertures was surprisingly small. Stimulation in the center (±12°) and within a horizontal aperture resulted in similarly negative correlation coefficients, whereas slightly more negative values were obtained for the largest stimulus aperture used. This suggests that central responses and possibly responses along the vertical meridian dominate the pattern-onset VEP[27] because it is presumably a vertical stripe in the center of the visual field that is affected by the projection abnormality.[23]

Consequences for the Investigation of Perception

Abnormal input to the albino visual cortex challenges cortical self-organization. To increase our knowledge of the processes underlying cortical self-organization, it is of particular interest to resolve how the abnormal cortical representation of the temporal retina actually contributes to visual perception. Although visual perception in human albinism has been investigated in a number of studies,[28–32] only one specifically addressed perception with the temporal retina.[33] In such studies it was particularly intriguing if evidence of different response patterns emerged because this appeared to reflect the diversity of cortical organization patterns known from animal studies.[34] Given the great intersubject variability in the extent of the projection abnormality, an alternative explanation of such results might be that the test stimulus has in some patients been applied to the normal part of the temporal retina and in others to the abnormal part. It is, therefore, vital for the correct assessment of perception mediated by the abnormal temporal retina to verify whether the part of the retina under investigation is actually affected by the projection abnormality.

Cortical Organization Pattern

In animal models of albinism, three different organization patterns of the abnormal representation in the visual cortex have been described.[34] One of these patterns, the midwestern pattern, is characterized by suppression of the abnormal geniculostriate input and appears to entail hemianopia of the temporal retina.[35,36] In each of the 16 subjects with albinism in the present study, cortical responses were evoked by the abnormally projecting temporal retina, as is evident from the negative correlation coefficients obtained. This is taken as evidence that the midwestern pattern was not established in these subjects. Indeed, recent fMRI-evidence suggests that the true albino pattern is established in human albinism.[23]

It is important to understand how visual perception is affected by the projection abnormality typical of albinism. Before such an investigation can be undertaken, the part of the visual field that is affected by the abnormality has to be identified. We devised a simple and objective electrophysiologic tool to identify, with high sensitivity and specificity, visual field locations that are affected by the projection abnormality.

Acknowledgments

The authors thank the German Research Council (DFG) for their support, Michael Bach for the kind permission to use his laboratory facilities, Guntram Kommerell for stimulating discussions, and the study subjects for their cooperation.

References

1. Lund RC. Uncrossed visual pathways of hooded and albino rats. *Science.* 1965;149:1505–1507.
2. Creel DJ. Visual system anomaly associated with albinism in the cat. *Nature.* 1971;231:465–466.

3. Kaas JH, Guillery RW. The transfer of abnormal visual field representations from the dorsal lateral geniculate nucleus to the visual cortex in Siamese cats. *Brain Res*. 1973;59:61–95.
4. Guillery RW, Okoro AN, Witkop CJ Jr. Abnormal visual pathways in the brain of a human albino. *Brain Res*. 1975;96:373–377.
5. Hedera P, Lai S, Haacke EM, et al. Abnormal connectivity of the visual pathways in human albinos demonstrated by susceptibility-sensitized MRI. *Neurology*. 1994;44:1921–1926.
6. Schmitz B, Kasmann-Kellner B, Schafer T, et al. Monocular visual activation patterns in albinism as revealed by functional magnetic resonance imaging. *Hum Brain Mapp*. 2004;23:40–52.
7. Morland AB, Hoffmann MB, Neveu M, Holder GE. Abnormal visual projection in a human albino studied with functional magnetic resonance imaging and visual evoked potentials. *J Neurol Neurosurg Psychiatry*. 2002;72:523–526.
8. Coleman J, Sydnor CF, Wolbarsht ML, Bessler M. Abnormal visual pathways in human albinos studied with visually evoked potentials. *Exp Neurol*. 1979;65:667–679.
9. Creel D, Spekreijse H, Reits D. Evoked potentials in albinos: efficacy of pattern stimuli in detecting misrouted optic fibers. *Electroencephalogr Clin Neurophysiol*. 1981;52:595–603.
10. Apkarian P, Reits D, Spekreijse H, van Dorp D. A decisive electrophysiological test for human albinism. *Electroenceph Clin Neurophysiol*. 1983;55:513–531.
11. Soong F, Levin AV, Westall CA. Comparison of techniques for detecting visually evoked potential asymmetry in albinism. *J Aapos*. 2000;4:302–310.
12. World Medical Association. Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2000; 284:3043–3045.
13. Bach M. The Freiburg Visual Acuity Test—automatic measurement of visual acuity. *Optom Vision Sci*. 1996;73:49–53.
14. Bach M. Bildergeschichte: Apples DrawSprocket in eigenen Programmen verwenden. *c't*. 1999;6:350–353.
15. Apkarian P, Shallo-Hoffmann J. VEP projections in congenital nystagmus; VEP asymmetry in albinism: a comparison study. *Invest Ophtholmol Vis Sci*. 1991;32:2653–2661.
16. Hoffmann MB, Seufert PS, Bach M. Simulated nystagmus suppresses pattern-reversal but not pattern-onset visual evoked potentials. *J Clin Neurophysiol*. 2004;115:2659–2665.
17. American Encephalographic Society. Guideline thirteen: guidelines for standard electrode position nomenclature. *J Clin Neurophysiol*. 1994;11:111–113.
18. Cooper J, Warshowsky J. Lateral displacement as a response cue in the Titmus Stereo test. *Am J Optom Physiol Opt*. 1977;54:537–541.
19. Sokol S. Abnormal evoked potential latencies in amblyopia. *Br J Ophthalmol*. 1983;67:310–314.
20. Davis AR, Sloper JJ, Neveu MM, Hogg CR, Morgan MJ, Holder GE. Electrophysiological and psychophysical differences between early- and late-onset strabismic amblyopia. *Invest Ophthalmol Vis Sci*. 2003;44:610–617.
21. Yu M, Brown B, Edwards MH. Investigation of multifocal visual evoked potential in anisometropic and esotropic amblyopes. *Invest Ophthalmol Vis Sci*. 1998;39:2033–2040.
22. Dorey SE, Neveu MM, Burton LC, Sloper JJ, Holder GE. The clinical features of albinism and their correlation with visual evoked potentials. *Br J Ophthalmol*. 2003;87:767–772.
23. Hoffmann MB, Tolhurst DJ, Moore AT, Morland AB. Organization of the visual cortex in human albinism. *J Neurosci*. 2003;23:8921–8930.
24. Warnking J, Dojat M, Guerin-Dugue A, et al. fMRI retinotopic mapping—step by step. *Neuroimage*. 2002;17:1665–1683.
25. Wandell BA. Computational neuroimaging of human visual cortex. *Annu Rev Neurosci*. 1999;22:145–173.
26. Apkarian P, Reits D. Global stereopsis in human albinos. *Vision Res*. 1989;29:1359–1370.
27. Shawkat FS, Kriss A. Effects of experimental scotomata on sequential pattern-onset, pattern-reversal and pattern-offset visual evoked potentials. *Doc Ophthalmol*. 1997;94:307–320.
28. Abadi RV, Pascal E. Visual resolution limits in human albinism. *Vision Res*. 1991;31:1445–1447.
29. Abadi RV, Pascal E. Incremental light detection thresholds across the central visual field of human albinos. *Invest Ophthalmol Vis Sci*. 1993;34:1683–1690.
30. Wilson HR, Mets MB, Nagy SE, Ferrera VP. Spatial frequency and orientation tuning of spatial visual mechanisms in human albinos. *Vision Res*. 1988;28:991–999.
31. Wilson HR, Mets MB, Nagy SE, Kressel AB. Albino spatial vision as an instance of arrested visual development. *Vision Res*. 1988;28: 979–990.
32. Yo C, Wilson HR, Mets MB, Ritacco DG. Human albinos can discriminate spatial frequency and phase as accurately as normal subjects. *Vision Res*. 1989;29:1561–1574.
33. St John R, Timney B. Sensitivity deficits consistent with aberrant crossed visual pathways in human albinos. *Invest Ophthalmol Vis Sci*. 1981;21:873–877.
34. Guillery RW. Neural abnormalities in albinos. *Trends Neurosci*. 1986;18:364–367.
35. Elekessy EI, Campion JE, Henry GH. Differences between the visual fields of Siamese and common cats. *Vision Res*. 1973;13: 2533–2543.
36. Garipis N, Hoffmann KP. Visual field defects in albino ferrets (*Mustela putorius furo*). *Vision Res*. 2003;43:793–800.