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Monocular Visual Activation Patterns in Albinism as Revealed by Functional Magnetic Resonance Imaging

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Abstract: Human albinism is characterized by a disturbance of the chiasmatic projection system leading to predominant representation of just one eye in the contralateral hemisphere. Patients show congenital nystagmus without perceiving oscillopsia. The purpose of the present study was to demonstrate the consequences of atypical chiasmatic crossing with monocular visual stimulation using functional magnetic resonance imaging (fMRI). Sixteen patients with albinism and fifteen normally pigmented controls were stimulated with a monocular visual activation paradigm using flickering checkerboards. In patients, we observed contralaterally dominated activation of visual cortices correlating to clinical albinism parameters. This confirms albinism as a continuous range of hypopigmentation disorders. Additionally, albinos showed activation of the superior colliculus and of visual motion areas although the stimulus was stationary. Activation of visual motion areas is due probably to congenital nystagmus without a conscious correlate like oscillopsia. *Hum Brain Mapp 23:40–52, 2004.* © 2004 Wiley-Liss, Inc.

Key words: albinism; central visual pathways; functional magnetic resonance imaging; visual motion areas; nystagmus

INTRODUCTION

In normally pigmented humans, each retina projects to both cerebral hemispheres by means of the chiasmatic hemidecussation. This arrangement allows binocular information from each hemifield to be processed in the contralateral cortical hemisphere (temporally ipsilateral, nasally contralateral), using information from both eyes and is thus a major basis for binocular vision and depth perception [Hubel and Wiesel, 1968]. Along the midsagittal plane, an overlap of retinal ganglion cell crossed and uncrossed projections contributes to binocular stereoscopic vision [Fukuda et al., 1989].

In patients with oculocutaneous or ocular albinism, this chiasmatic projection pattern is disturbed and the line of decussation is shifted to the temporal aspects of the retina. More retinal ganglion cells cross to the contralateral side, leading to predominant representation of just one eye in the contralateral hemisphere [Guillery et al., 1975]. The magnocellular pathway is affected to a larger degree [Kirk, 1976; cited in Lund, 1978]. Underlying mechanisms for this chiasmatic arrangement are not exactly known [Guillery, 1996], but most likely involve disturbances in the developmental timing of the albino retina [Dräger, 1985; Ilia and Jeffery, 1999; Jeffery, 2001]. At the lateral geniculate nucleus, fibers from parts of the temporal retina terminate at the wrong side

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of the brain in a mirror-reversed pattern of the normal representation of the visual field [Sherman and Guillery, 2001].

Using monocular stimulation, albinism can be confirmed by visually evoked potentials (VEPs) [Apkarian et al., 1983]; however, there are VEP studies that do not confirm these findings in all patients with albinism [Jarry et al., 2000]. Because the varying pigmented types of oculocutaneous albinism and ocular albinism are not necessarily distinct, providing a continuous range of hypopigmentation [Käsmann-Kellner et al., 1999; Passmore et al., 1999], it seems reasonable to assume that the extent of crossing varies with the severity of hypopigmentation. In addition, it may not be possible to show this atypical crossing with monocular VEPs in certain cases of almost normal arrangements of the chiasmatic decussation.

Functional magnetic resonance imaging (fMRI) provides higher spatial resolution than do studies of evoked potentials and thus might reveal more subtle differences. In addition, it is possible to quantify the extent of activation in certain parts of the brain and to correlate these with clinical parameters.

To apply fMRI measurements in patients with albinism, the various anomalies of their visual system must be taken into account [Dräger, 1986]. From animal studies, it is known that there is a profound rod deficit [Grant et al., 2001] and an altered visual field representation [Hubel and Wiesel, 1971]. For the purpose of effective fMRI in human albinos, reduction of visual acuity seems to remain more functionally important. This reduction is due to a combination of foveal hypoplasia [Elschnig, 1913], lack of binocular vision, optic nerve hypoplasia, nystagmus, strabismus [Lacour and Ortonne, 1992], uncorrected refractive errors, and amblyopia [Lorenz, 1997; Spedick and Beauchamp, 1986; Taylor, 1978]. The symptoms render it very difficult to carry out complex visual experiments, especially in the unusual circumstances inside a magnetic resonance scanner. We therefore decided to rely on simple monocular checkerboard stimulation in a standard fMRI block design. As patients with albinism demonstrate a congenital nystagmus [Collewijn et al., 1985], mapping of functional subdivisions of the visual cortex is compromised unless the amplitude of nystagmus is small [Morland et al., 2002]. The definite reason for this nystagmus remains unclear, but congenital fixation nystagmus is a common sign in all congenital visual impairments. As in other congenital visual impairments, human albinos do not suffer from oscillopsia despite the constant retinal image shift. They are able to perceive motion although motion perception thresholds are higher [Abadi et al., 1999]. The compensation mechanism for the retinal image motion is unclear, but probably an extraretinal cancellation mechanism using efference copies is at least partly responsible [Tusa, 1999].

Our purpose was to confirm and quantify the extent of atypical chiasmatic crossing in a larger albino population and to reveal the consequences as general visual activation patterns in albinos as compared to normally pigmented subjects using fMRI.

SUBJECTS AND METHODS

Subjects

A standardized morphologic evaluation was carried out for 16 patients (11 female, all right-handed according to Oldfield [1971]; mean age, 31.0 years; standard deviation [SD], 3.5 years) with oculocutaneous or ocular (patient W.K.) albinism [Käsmann-Kellner et al., 1999]. This included assessment of visual function and binocular interaction/stereopsis, evaluation of individual nystagmus, definition of the degree of iris transillumination, hypopigmentation of the retinal pigment epithelium, foveal hypoplasia, and optic nerve head anomalies (e.g., dysplastic optic nerve head [ONH]), and the evaluation of refractive errors (anterior and posterior segment changes were morphologically graded). Clinical history was obtained with respect to photophobia, skin type, inability to tan, and family history of albinism. Of 16 patients, 8 were defined as OCA1 (tyrosinase gene-related oculocutaneous albinism), 4 were genetically diagnosed as OCA2 (P gene-related OCA; pink-eye dilution gene), 1 patient presented with OA1 (ocular albinism 1), and 4 patients remain under evaluation. In addition, 15 normally pigmented age- and gender-matched controls (10 female, all right-handed according to Oldfield [1971]; mean age, 26.2 years; SD, 2.6 years) were clinically evaluated with the same protocol. All subjects gave written informed consent according to the declaration of Helsinki. The study was in accordance with local institutional review board.

Concurrent neurologic disease has been ruled out before the study by neurologic examination and standard magnetic resonance (MR) brain scans without contrast media using a turbo spin echo T2 (23 slices, voxel size $1 \times 1 \times 5$ mm^3) and turbo flash T1-weighted sequence (magnetization prepared rapid acquisition of gradient echo [MPRAGE]; $1 \times 1 \times 1$ mm^3 voxel size) [Mugler and Brookeman, 1990], which were also used for individual anatomic reference.

Functional MR Scanning

All functional images were acquired in a 1.5-T Magnetom Vision (Siemens, Erlangen, Germany) whole-body MR scanner system equipped with a head volume coil. We used a echo planar imaging (EPI) mosaic sequence with 5-mm slice thickness and 3.3×3.3 mm^2 pixel size covering the whole brain (TR = 2.5 sec; TE = 60 msec; 24 slices, axial direction parallel to the anterior commissure–posterior commisure (AC–PC) line).

Each eye received monocular stimulation in two separate sessions by covering one eye with a light-blocking occlusion skin patch as used normally in amblyopia treatment. Visual inspection of the open eye after application of the skin patch did not reveal any alteration of the nystagmus. Stimulation started with the left eye.

Stimuli were applied by flickering checkerboards providing 100% contrast with 2-Hz frequency for visual stimulation. Stimuli were presented using a beamer standing outside of the scanner room and projecting through a window on a mirror mounted on the head coil in front of the subjects'

eyes. Visual angle of the entire matrix was 39.9 degrees horizontally and 23.0 degrees vertically. The checkerboards consisted of a 7 × 4 matrix with 5.7-degree visual angle in either direction for each subunit. There was no other source of light in the MR room.

Stimulation was done within a block design with each epoch lasting 15 sec (equivalent to 6 whole-brain fMRI volume acquisitions) and 10 repetitions for each session. During resting epochs, a black screen was presented and subjects were told to open and close their eyes by a computer-generated voice over a MR-suitable headset.

The stimulation paradigm was run on a 600 MHz Dual Pentium III-based computer with 512 MB RAM and a high-resolution SVGA chipset (1,024 × 768 pixel) using LabView (National Instruments, Austin, TX). Stimulation was triggered externally by the MR scanner.

STATISTICAL ANALYSIS

Statistical analysis was carried out with Statistical Parametric Mapping (SPM; Wellcome Department of Cognitive Neurology, London, UK; online at http://www.fil.ion.ucl.ac.uk) executed in MatLab 5.3 (Mathworks, Natick, MA). All individual images were slice timed, corrected for deformations [Andersson et al., 2001] and motion artifacts (range of estimated individual head motion, 0.2–1.2 mm according to SPM realignment output) by realignment to the first volume of the first session. A sinc interpolation was used to reslice the realigned volumes. All images were spatially normalized to a standard template of $2 \times 2 \times 2$ mm^3 voxels. Images were then smoothed spatially with an 8-mm full width half maximum (FWHM) isotropic Gaussian kernel. For each session, the variance of each voxels was estimated according to the general linear model using a boxcar model convoluted with the hemodynamic-response function as the predictor. Conditions defining the onset of active and resting epochs as events were added to the design matrix, because onset of epochs included acoustical commands. These covariates were left as covariates of no interest. Images were adjusted for global effects, and low-frequency drifts were removed via a high-pass filter using low-frequency cosine functions with cut-off of 67 sec [Holmes et al., 1997]. Individual regionally specific effects between active and resting epochs were calculated using linear contrasts, producing a *t*-statistic for each voxel. To consider interindividual variance, group analyses were computed using a random-effects model. Group analysis across subjects involved a one-sample *t*-test within groups and directed single-tailed two-sample *t*-tests between groups on images generated by individual fixed-effects analyses of activation versus rest. Within group comparisons between left and right eye stimulation were computed by paired *t*-tests. For random effects, group analysis voxels were thresholded at a level of $P < 0.001$ (uncorrected). Clusters of significant voxels were thresholded at a level of $P < 0.05$ corrected for multiple comparisons according to the theory of Gaussian random fields.

Additional group analyses using a fixed-effects model were computed. Group differences were calculated by specifying the appropriate contrasts. For voxels from these analyses, a threshold of $P < 0.05$ (corrected) was applied. Clusters of significantly activated voxels were thresholded at a level of $P < 0.05$ (corrected). Areas were labeled using the nomenclature of Talairach and Tournoux [1988] and Brodmann [1909].

The magnitude of activation was quantified by using β values of local maxima within activated clusters.

The extent of activation was quantified for each hemisphere and eye stimulation. For each single subject, the number of activated voxels above a threshold of $P < 0.001$ (uncorrected) derived from clusters with a level of $P < 0.05$ (corrected) was counted for each hemisphere separately. Individual results have been masked with the result of group contrasts to exclude voxels outside visual areas. The ratio of crossed to uncrossed activation was calculated for each eye of each subject separately using the following formula [e.g., Tamada et al., 1999]:

$$\text{Crossing ratio} = \frac{\text{Activation}_{\text{ipsi}} - \text{Activation}_{\text{contra}}}{\text{Activation}_{\text{ipsi}} + \text{Activation}_{\text{contra}}}$$

The mean of crossing ratios of the left and right eye was calculated for correlations with general clinical hypopigmentation parameters. For comparisons of left and right hemispheric activations within and between groups, the individual number of activated voxels of either hemisphere was determined relative to the number of activated voxels on both hemispheres to compensate for general activation levels that were different between individuals. Statistical tests were calculated using SPSS 8.0 (SPSS Inc., Chicago, IL).

RESULTS

Normally Pigmented Controls

Clinical examination showed no evidence for hypopigmentation disorders in any control group subject. Random-effects analysis (RFX) of monocular visual stimulation in the normally pigmented control group showed bilateral activation of visual cortex. Effect sizes at local maxima in the left and right V1 region numerically indicated a mild predominance of the contralateral hemisphere (mean ± SD of β values: right eye stimulation, 1.47 ± 0.37 ipsilaterally vs. 1.59 ± 0.40 contralaterally; left eye stimulation: 1.18 ± 0.34 ipsilaterally vs. 1.40 ± 0.49 contralaterally). Differences of effect sizes were not significant (paired *t*-tests, $P > 0.10$). Activated areas included primary visual fields around the occipital pole and calcarine fissure as well as parts of right parietal cortex (Fig. 1A). In addition, activation of lateral geniculate nucleus and frontal regions involving frontal eye fields were observed (Table I). There was no activation of explicit visual motion areas, such as the hMT/V5 region.

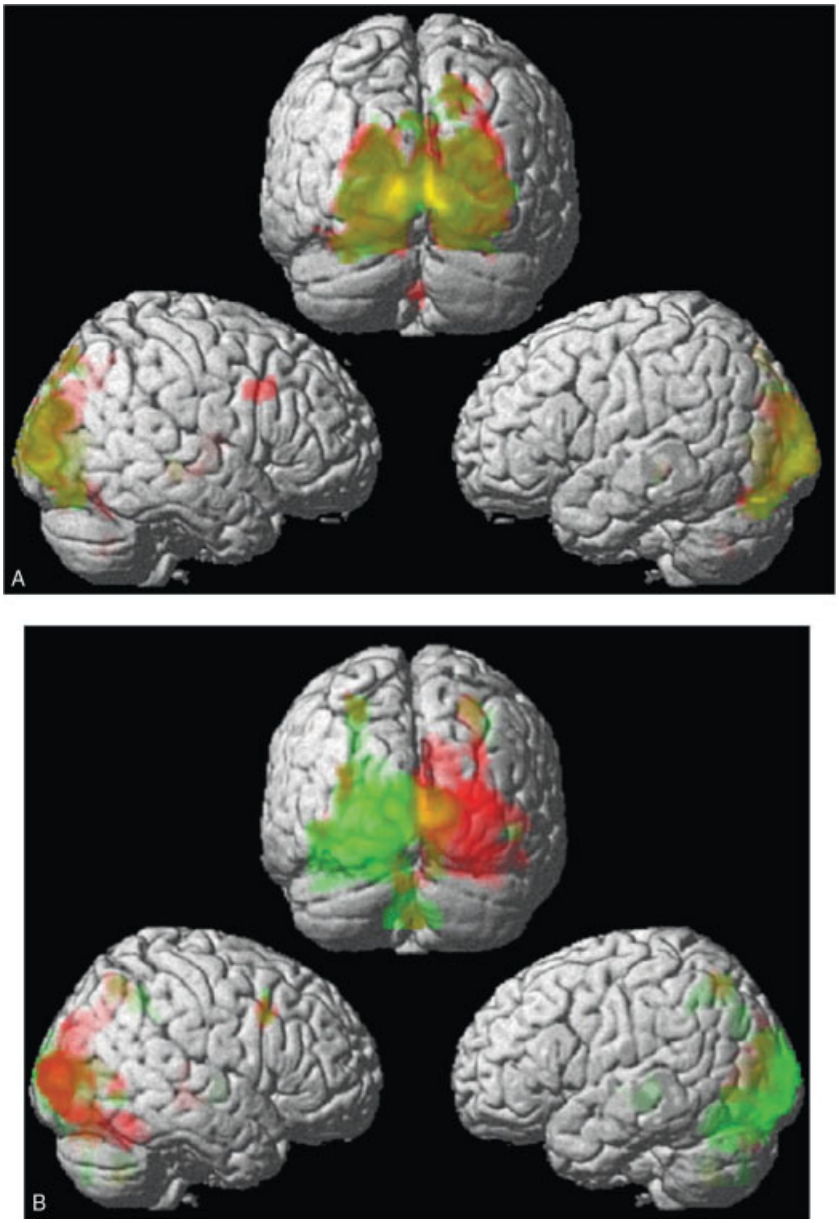

Figure 1.
A: Activation of controls. 3D surface projection on a standardized T1 template with activations of the normally pigmented control group. Red, monocular stimulation of the left eye; green, monocular stimulation of the right eye. Matching areas add up to yellow. Activation is shown in primary and secondary visual areas around the occipital pole extending to the right parietal lobe. Activation of LGN, right frontal eye field, and inferior cerebellar vermis is also shown. **B:** Activations of patients with albinism. 3D surface projection on a standardized T1 template with activations of the albinism group. Red, left eye stimulation; green, right eye stimulation. There is a clear contralateral dominance of activation of visual cortex and LGN. Activation of visual motion areas hMT/V5 and superior parietal lobule is shown on both hemispheres for each stimulated eye.

Patients With Albinism

Results of the clinical examination are detailed in Table II. There was no patient with aperiodic alternating nystagmus (APAN). Group analysis of patients with albinism yielded an activation of visual cortex that was unbalanced between ipsi- and contralateral hemispheres, where the contralateral hemisphere showed a much larger area of activation (Fig. 1B and Fig. 2). The cortical activation patterns were different and extended further into the temporal lobe, especially the fusiform gyrus.

In human albinos, right parietal cortex showed activation in the same regions as was observed in controls. The lateral geniculate nuclei (LGN) showed predominant contralateral activation. The contralateral superior colliculi were also activated (Fig. 3).

Comparing left and right eye stimulation within the albino group by paired *t*-tests confirmed that contralateral activation was stronger for primary visual areas as well as the LGN and superior colliculus (Fig. 4).

Frontal regions including frontal eye fields were also activated in the albino group but to a lesser extent than that in controls, and only the right frontal eye field was significant.

A striking difference between albinos and controls was the activation of ipsi- and contralateral visual motion area hMT/V5 in albinism. The location of this region was confirmed by a second fMRI paradigm using moving dots for

TABLE I. Random-effects results for within-group analysis of patients with albinism and controls

Stimulation	*x*	*y*	*z*	Anatomic regions	BA	Z
Albinos						
Left eye	8	−94	8	Right cuneus	18	6.3
	−8	−84	6	Left cuneus	18	5.1
	18	−28	−2	Right lateral geniculate nucleus	—	5.1
	8	**−32**	**−8**	**Right superior colliculus**	—	**4.0**
	0	−60	−44	Cerebellar tonsil	—	4.3
	48	**−62**	**2**	**Right inferior temporal gyrus**	**19**	**4.3**
	−24	−66	50	Left superior parietal lobule	7	4.3
	54	14	40	Right middle frontal gyrus	6	4.1
	−30	−90	22	Left superior occipital gyrus	19	3.8
	−42	**−72**	**−4**	**Left inferior temporal gyrus**	**19**	**3.6**
Right eye	−2	−94	−8	Left occipital lobe, lingual gyrus	18	6.7
	16	−88	4	Right lingual gyrus	18	5.1
	−16	−30	−4	Left lateral geniculate nucleus	—	5.2
	−4	**−32**	**−6**	**Left superior colliculus**	—	**2.9**
	−24	−68	52	Left parietal lobe, precuneus	7	3.5
	4	−58	−42	Cerebellar tonsil	—	5.2
	46	**−60**	**−6**	**Right inferior temporal gyrus**	**19**	**3.4**
	−44	**−72**	**−4**	**Left inferior occipital gyrus**	**19**	**4.7**
	50	14	48	Middle frontal gyrus	6	3.3
	26	−60	54	Right parietal lobe, precuneus	7	3.1
	14	−10	2	Right thalamus	—	3.2
Controls						
Left eye	12	−92	−6	Right inferior occipital gyrus	17	6.1
	−2	−88	−6	Left lingual gyrus	18	5.7
	22	−28	−6	Right lateral geniculate nucleus	—	4.2
	−16	−32	−4	Left lateral geniculate nucleus	—	3.9
	0	−62	−42	Cerebellar tonsil	—	4.0
	14	−78	54	Right precuneus	7	4.9
	−24	−54	50	Left precuneus	7	3.0
	54	8	34	Right middle frontal gyrus	9	3.9
	10	−8	6	Right thalamus, ventral lateral nucleus	—	5.1
Right eye	14	−94	−6	Right lingual gyrus	17	6.1
	−2	−86	−6	Left lingual gyrus	18	6.0
	22	−28	−4	Right lateral geniculate nucleus	—	4.4
	−20	−28	−10	Left lateral geniculate nucleus	—	3.7
	22	−78	46	Right precuneus	7	4.1

Stereotactic coordinates; x, left-right; y, anterior-posterior; z, inferior-superior distance in millimeters from the anterior commissure. Z-score denotes activation level. Non-matching regions between albino and control group are shown in bold; BA, Brodmann's area.

explicit motion stimulation within the same albino and control subjects.

Group Comparisons

RFX comparing groups of albinos and normally pigmented controls showed that activation of ipsilateral cortex was more pronounced in controls than in albinos. This result was the same for both eyes. The activation was confined to the occipital pole corresponding to the foveal representation (Fig. 5).

The inverted contrast (albinos minus controls) showed a global maximum in the contralateral fusiform gyrus (Table III), which was consistent with the different activation pattern demonstrated above in the single group analysis. Activation in visual motion areas did not reach suprathreshold levels in this group comparison.

Comparing groups by fixed-effects analysis (FFX), which was more sensitive but confined to statistical inference for the study sample, showed suprathreshold activation in different visual motion areas (Table IV) including hMT/V5 (Fig. 6) when comparing albinos minus controls. In addition, FFX analysis showed activation of ventral areas in the calcarine fissure for the albino group. A third, well-defined area activated more in albinos than in controls was the superior parietal lobule bilaterally, which was consistent with RFX of the albino group. Inverting the contrast (controls minus albinos) demonstrated predominant activation of the foveal representation area at the occipital pole.

TABLE II. Details of morphologic and functional evaluations of the patients with albinism and results of the mean crossing ratio

Initials	Gender	Visual acuity			Skin	Skin pigmentation	Hair	Hair pigmentation	Iris translucency	Fovea	ONH	Mean crossing ratio
		Right eye	Left eye	Mean								
G.B.	Female	0.1	0.1	0.1	1	1	3	2	3	3	3	−0.2
F.D.	Female	0.3	0.2	0.25	3	2	5	2	3	4	4	−0.03
A.K.	Female	0.07	0.07	0.07	1	1	3	2	4	4	4	−0.39
M.K.	Male	0.1	0.2	0.15	2	1	8	2	3	4	4	−0.24
W.K.	Male	0.2	0.2	0.2	5	3	9	2	3	3	3	−0.58
Sa.K.	Female	0.1	0.1	0.1	2	1	4	1	3	3	4	−0.28
J.K.	Male	0.16	0.16	0.16	1	1	3	1	4	3	4	−0.53
Su.K.	Female	0.4	0.3	0.35	2	1	5	1	2	3	4	−0.04
K.L.	Female	0.1	0.1	0.1	1	1	1	1	4	3	3	−0.37
K.M.	Male	0.1	0.05	0.08	1	1	1	1	4	4	4	−0.23
H.M.	Male	0.01	0.01	0.01	1	1	1	1	4	4	4	−0.58
C.P.	Female	0.2	0.2	0.2	1	1	5	2	3	3	2	−0.12
A.R.	Female	0.14	0.14	0.14	1	1	3	1	3	3	3	−0.2
B.S.	Female	0.1	0.1	0.1	1	1	3	1	4	3	4	−0.49
P.S.	Female	0.1	0.1	0.1	1	1	1	1	4	4	3	−0.41
V.C.	Female	0.1	0.05	0.08	1	1	1	1	4	4	4	−0.46

Skin: 1, white, no tanning; 2, white, maybe pigmented naevi, some tanning; 3, pale, some visible tanning; 4, pale, good tanning; 5, normal, good tanning. Pigmentation of skin during life: 1, none; 2, some; 3, distinct. Hair color: 1, completely white; 2, silvery white; 3, white with yellowish touch; 4, whitish blonde; 5, pale blonde; 6, medium blonde; 7, dark blonde; 8, red, red-blonde; 9, medium brown; 10, dark brown, black. Pigment formation in hair during life: 1, not at all; 2, some; 3, distinct. Degree of iris translucency: 1, peripheral punctual iris translucency (only visible with confocal light, slit lamp); 2, diffuse peripheral iris translucency, near pupillar border not translucent; 3, diffuse peripheral iris translucency, lens margin clearly visible through iris, pupillary margin not translucent; 4, complete iris translucency including the pupillary margin. Degree of hypopigmentation of the retinal pigment epithelium and of foveal hypoplasia: 1, peripheral retinal hypopigmentation, foveal structures visible; 2, peripheral distinct and centrally visible hypopigmentation, macular reflex visible, foveal reflex not visible; 3, pronounced peripheral and central hypopigmentation, foveal and macular hypoplasia; 4, Grade 3 plus atypical choroidal vessels crossing the presumed macular region. Degree of morphologic anomaly of optic nerve head (ONH): 0, ONH not pathologic; 1, ONH pale, normal size; 2, ONH small, color is vital; 3, ONH small and pale; 4, dysplasia of ONH.

Calculation of Crossing Ratios and Clinical Correlation

For each subject's eye and hemisphere, the number of activated voxels was quantified, and means and standard deviations for distributions within each group were calculated.

Control data

In controls, the extent of activation on the right hemisphere (55 ± 6% for left eye stimulation, 56 ± 3% for right eye stimulation) was significantly larger than that on the left hemisphere (45% for left eye stimulation vs. 44% for right eye stimulation), regardless of the eye stimulated (Fig. 2A). This was due to additional recruitment of inferior parietal regions as shown in Figure 1, probably reflecting the visuospatial nature of our stimuli.

Patient data

Comparing the extent of ipsi- and contralateral activations for the albino group, laterality effects were more pronounced. Left monocular stimulation showed 72 ± 11% of all voxels activated on the right hemisphere and 28 ± 11% on the ipsilateral hemisphere. Right monocular stimulation showed 60 ± 10% of activated voxels on the contralateral, left hemisphere whereas 40 ± 10% were ipsilaterally active (Fig. 2B).

Again, significance of laterality effects were tested in the same manner as that used for controls (Wilcoxon signed rank tests; $P < 0.01$). Taken together, there was a clearcut pattern of significant contralateral dominance observed in the albino group regardless of the eye stimulated.

Ratios of crossed to uncrossed activation were calculated such that −1 indicated crossed activation only, 0 indicated equal crossed and uncrossed activation, and 1 indicated only uncrossed activation. The mean crossing ratio for the albino population was −0.32 ± 0.18. Mean crossing ratio for the control population was 0.01 ± 0.06 (Fig. 2B). The difference between the crossing ratios for the albino and normally pigmented population was again significant at $P < 0.001$ (Mann–Whitney test).

Mean crossing ratios of the albino population correlated with clinical parameters, particularly with iris translucency (Pearson correlation −0.660; $P < 0.01$) and mean visual acuity (Pearson correlation 0.583; $P < 0.05$; Fig. 7). Because all patients in the study showed a high grade of retinal hypopigmentation and optic nerve head dysplasia (Table II),

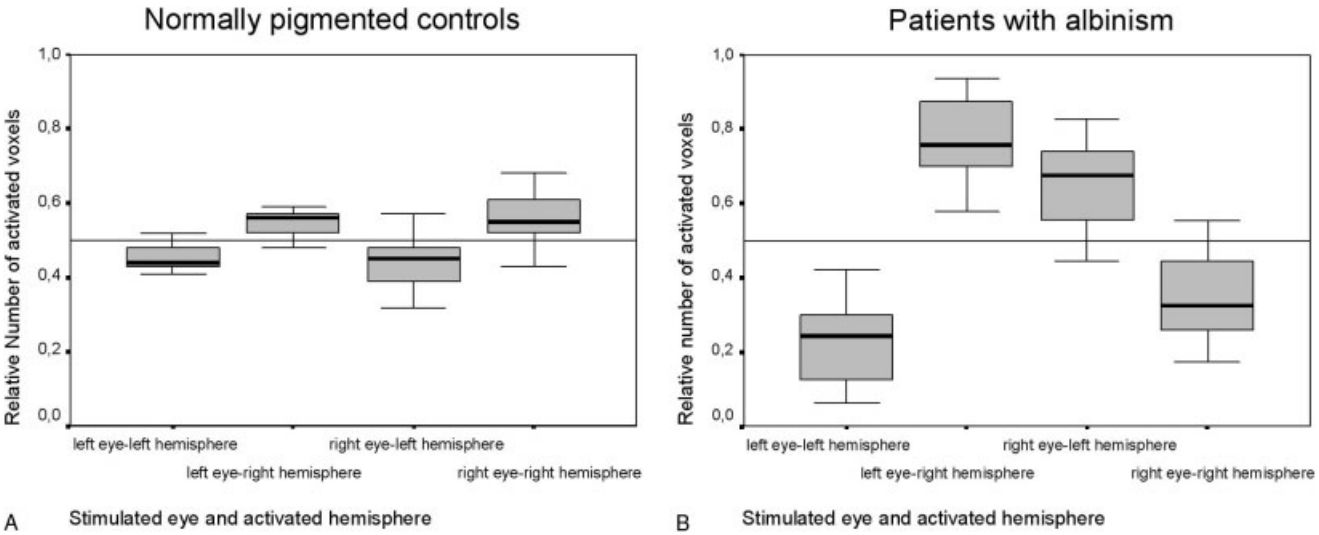

Figure 2.

A: Quantification of activation of controls. Voxel counts of normally pigmented controls showing the number of activated voxels in one hemisphere relative to the number of activated voxels in both hemispheres for monocular stimulation. Left eye-left hemisphere means activated voxels in the left hemisphere for monocular stimulation of the left eye. Boxplots show median, quartiles, and extremes. Right hemisphere shows more extended clusters regardless of the eye stimulated. **B:** Quantification of activation of patients with albinism (voxel counts for the albinism group, abbreviations, and definitions as in A). The more extended differences between hemispheres for stimulation of either eye are partly a consequence of the paradigm used and reflect the shift to the right hemisphere seen already in controls.

correlations with respect to these parameters were not possible.

DISCUSSION

We studied monocular activation patterns in human albinos after validating our fMRI paradigm in a normally pigmented control group for comparisons. All findings were consistent for stimulation of either the right or the left eye.

We confirmed that in human albinos each eye is represented almost completely on the contralateral hemisphere. From fMRI data, we calculated the ratio of crossed to uncrossed activation. This was interpreted as a measure to index the extent of chiasmatic crossing. This index correlated significantly with clinical albinism parameters. In contrast to controls, albinos showed activation of the superior colliculi and visual motion areas without explicit motion stimulation or oscillopsia.

Crossing Ratio in Normal Controls

Previous findings on contralateral dominance during monocular visual stimulation are equivocal. Although some found no contralateral dominance [Miki et al., 1996; Rombouts et al., 1998], others showed significant functional asymmetry [Toosy et al., 2001].

Regarding the magnitude of activation, we found a moderate but not statistically significant contralateral dominance; however, the extent of spatial activation did not show any hemispheric dominance. We therefore conclude that there might exist a predominance of contralateral activation even in normally pigmented subjects. This effect is obviously very small, however, and does not seem to confound with the interpretation of results from the albino group. Moreover, the effect is associated only with the magnitude of activation. When considering the extent of spatial activation, this effect is absent. For analysis of data from the albino group, we therefore concentrated on extent of spatial activation as the relevant parameter.

Crossing Ratio in Human Albinos

Human albinos showed predominant contralateral activation of lateral geniculate nuclei and visual cortical areas. This is in good agreement with previous findings on atypical chiasmatic crossing of retinogeniculate fibers in human albinos [Guillery, 1971, 1974; Guillery et al., 1975; Hedera et al., 1994; Hubel and Wiesel, 1971]. The contralateral activation was larger for stimulation of the left eye (Fig. 2B). This is caused by the additional recruitment of right parietal cortex due to the visuospatial nature of the stimuli used. For correlation of a crossing index with clinical parameters we have therefore chosen the mean crossing ratio, which eliminates the shift toward right hemispheric superiority in activation. The crossing ratio was interindividually different, especially in the albino group (Fig. 7B,C) and correlated with clinical albinism parameters such as iris translucency or visual acuity. When considering our definition of the crossing ratio, which is between -1 and 1, it is obvious that a

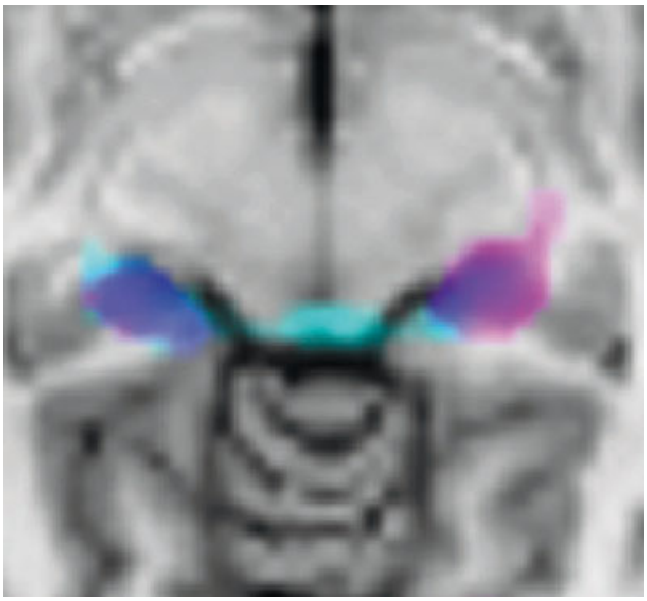

Figure 3.
Comparison of midbrain activation between albinos and controls. Color-coded midbrain activation patterns from albinos and controls. Axial section zoomed to the midbrain. Cyan shows activation of the albino group comprising the LGN and superior colliculi. Magenta shows activation of the control group representing the LGN, but no activation of the superior colliculi. Matching areas add up to blue.

linear correlation can be applied only to a certain range of visual acuity. We therefore conclude that the linear correlation found is true only for the albino population within the biologically defined range of low visual acuity that is typical for albinism. Interindividual differences confirm that albinism comprises a spectrum of hypopigmentation disorders, which could also explain discrepant results in studies on the diagnostic value of visually evoked potentials in patients with albinism [Apkarian et al., 1983; Jarry et al., 2000].

Foveal Representation

Comparison of the local patterns of activity within primary visual areas between groups revealed that controls activated the occipital pole to a larger extent in correspondence with foveal representation. Activation of primary visual areas in the albino group was more rostrally located in the calcarine sulcus, due probably to the foveal hypoplasia in human albinos (Fig. 8) leading to reduced activation of corresponding cortical areas. On the other hand, congenital nystagmus in this group seemed to cause an activation of expanded retinal areas, leading to a generally larger activated cortical area [Mason et al., 1991].

Inferior Temporal Activation

Albinos showed more inferior temporal activation than did controls, especially comprising the fusiform gyrus. From previous experiments [e.g., Barton, 1998] this area is known for object recognition, which was not part of the activation paradigm used in our study. To explain the fusiform activation, at least two interpretations are possible. Activation in this area might reflect a different type of visual processing or different morphologic organization of visual areas in albinos; however, definitive conclusions cannot be deduced from our data.

Activation of Visual Motion Areas

Albinos showed activation of visual area hMT/V5 known for motion processing [Freitag et al., 1998; Watson et al., 1993; Zeki et al., 1991; Zihl et al., 1983]. This was observed despite missing motion stimulation and despite a lack of subjective motion perception by the subjects (no oscillopsia in congenital nystagmus). The location of activation in our study showed good agreement with previously reported coordinates for hMT/V5 [Sunaert et al., 1999] and was confirmed additionally by a visual motion task using moving dots in the same group of patients and controls. This activation is due most probably to the fact that continuous

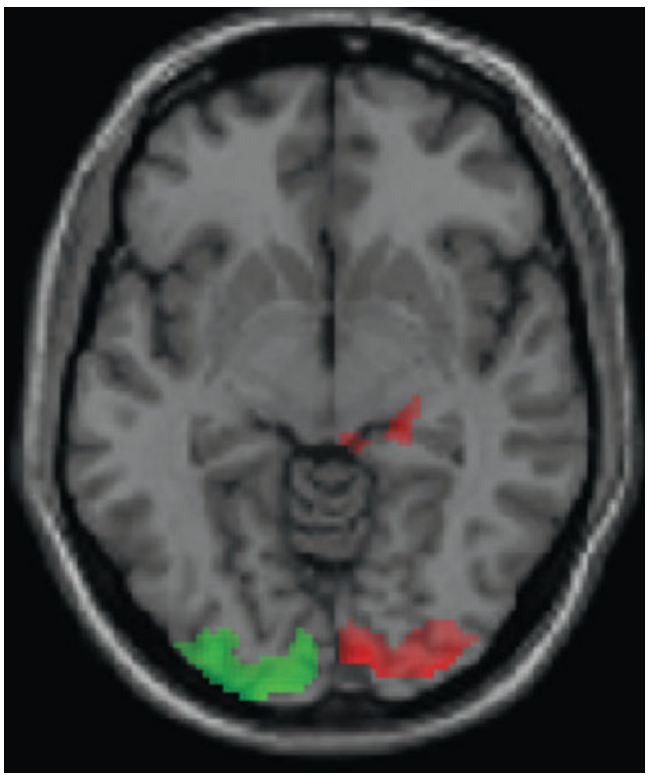

Figure 4.
Paired *t*-tests of left vs. right eye within albino group. Results of paired *t*-tests within albino group comparing left and right eye stimulation. The figure shows an axial section through the occipital pole, LGN, and superior colliculi demonstrating contralateral activation to be dominant. Red encodes voxels that are activated more by left eye stimulation, and green by right eye stimulation.

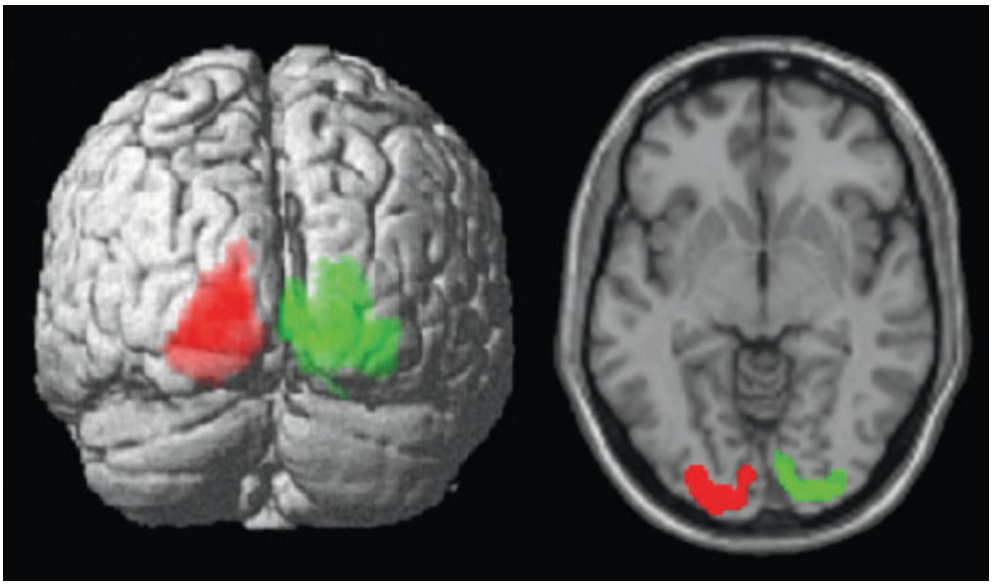

Figure 5.
A *t*-test comparison between controls and albinos. Surface projection and axial reconstruction along the calcarine sulcus, showing results of group comparisons. Contrasting activity between groups (directed single-tailed *t*-test) demonstrates the ipsilateral superiority in controls due to different crossing ratios. Red, left eye stimulation; green, right eye stimulation.

retinal shift caused by congenital nystagmus in albinos is already sufficient to elicit activation of hMT/V5. Activation of hMT/V5 alone, however, is not sufficient to cause conscious perception of visual motion, at least in albinos, because albinos do not suffer from oscillopsia [Abadi et al., 1999].

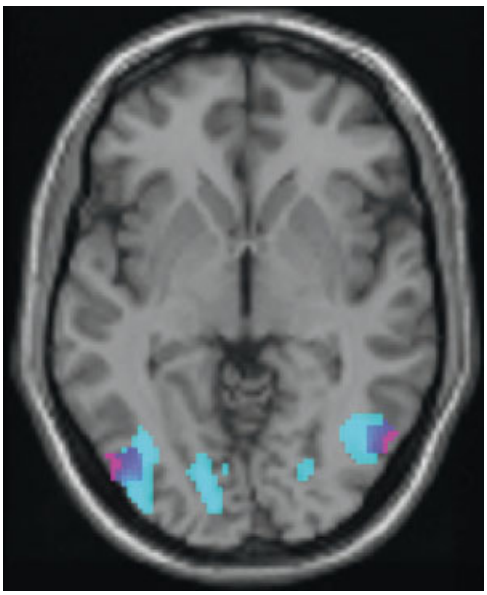

Figure 6.
Confirmation of localization of V5 activations in patients with albinism. Axial section through the temporal and occipital lobes. Activations in cyan show results of the fixed effects contrast of albinos minus controls. The activated areas extend to visual motion area hMT/V5 on both hemispheres. Localization of hMT/V5 was confirmed by a second fMRI paradigm in the same patient group using moving dots. Results of this additional experiment are shown in magenta. Matching areas add up to blue.

For normal controls, it has been discussed that human visual motion area hMT/V5 is able to cause a conscious visual motion perception on its own without V1 interaction [Barbur et al., 1993], and that lesions to hMT/V5 result in cerebral akinetopsia [Zeki et al., 1991]. We therefore conclude that retinal image movement is an adequate stimulus for hMT/V5 involvement. For individual nystagmus parameters, motion perception is suppressed in albinos despite hMT/V5 activation. Similar findings of sustained extrastriate activation despite missing motion perception have been reported from studies of hemianopic patients [Goebel et al., 2001]. The suppression could be mediated by prefrontal and parietal regions, which were more activated in albinos than in controls.

The more sensitive fixed effects between-group comparisons confirmed the hMT/V5 activation and revealed additionally activated regions for the albino group that have been described recently as being also motion responsive [Sunaert et al., 1999]. Activation of the superior parietal lobule close to the anterior intraparietal sulcus, the left middle frontal gyrus close to the superior frontal sulcus, and the middle occipital gyrus corresponding to hV3A were described especially as motion sensitive. These regions correspond to activations observed in our study, providing further evidence for the interpretation that pure retinal image movement causes activation of motion-responsive regions even without conscious motion perception.

Activation of the Superior Colliculus

Predominant crossed activation of the superior colliculi was observed in human albinos. The superior colliculi are rather small structures and certainly very close to the physical resolution limit of our fMRI sequence, especially after

TABLE III. Random effects group comparisons between patients with albinism and controls

Stimulation	*x*	*y*	*z*	Anatomic region	BA	Z
Albinos > Controls						
Left eye	40	−54	−18	Right fusiform gyrus	37	3.84
Right eye	−42	−60	−18	Left fusiform gyrus	37	3.67
	−40	−82	−10	Left inferior occipital gyrus	18	4.3
Controls > Albinos						
Left eye	−14	−100	2	Left cuneus	18	5.97
Right eye	16	−94	−8	Right lingual gyrus	17	6.53

Stereotactic coordinates: *x,* left-right; *y,* anterior-posterior; *z,* inferior-superior distance in millimeters from the anterior commissure. Z-score denotes activation level; BA, Brodmann's area.

spatial filtering. Activation of superior colliculus, however, has been reported in several recent fMRI studies [Buchel et al., 1998; DuBois and Cohen, 2000; Grön et al., 2000]. In addition, activation was observed for each eye separately, thereby replicating the result and rendering it more reliable.

Recent findings on activation of superior colliculi [Moschovakis, 1996; Munoz et al., 1991; Waitzman et al., 1991] view this structure to be part of the local feedback loop of the saccadic system. Generally, the mechanism assumed for that structure is that a signal on actual eye position is compared to a desired eye position signal and that the difference is conveyed to burst generators. Because actual and desired eye positions in human albinos mismatch due to continuous retinal slip, stronger involvement of superior colliculi by the albino group seems reasonable. The activation, however, allows no conclusion as to whether the superior colliculus might be involved in generating nystagmus per se, or whether it is activated by trying to compensate the retinal slip produced by the nystagmus.

Frontal Activation

Under non-constrained viewing conditions, observers usually carry out orientating saccades. Our paradigm implied constant fixation of the center of the flickering checkerboard, forcing the subjects to actively suppress large orientating saccades and to direct spatial attention to the visual stimulus. Other studies [Law et al., 1997; Nobre et al., 1997] showed previously that saccade suppressing and focusing of visual attention cause activation in the same frontal compartment as that observed in our study. We therefore consider this the most probable explanation for the frontal activation. Patients with albinism showed the same frontal activation patterns as controls did, providing neuroimaging evidence that focusing spatial attention to certain locations is possible in albinos despite their fixation nystagmus and is mediated probably by the same frontal structures as that in normally pigmented controls.

CONCLUSION

The ratio of ipsi- to contralateral visual cortex activation after monocular stimulation was interindividually different in human albinos and correlated with clinical albinism parameters. Despite a stationary stimulus, human albinos showed an activation of visual motion areas without a conscious correlate such as oscillopsia, due most probably to congenital nystagmus. Activations of superior colliculi in albinos are suggestive of their involvement in congenital nystagmus. Combining the detailed results from experimental animals with the advantages of upcoming high-spatial resolution fMRI may help to elucidate further the specific functional roles of the cortical network observed in albinos.

TABLE IV. Albino > controls fixed effects group analysis between patients with albinism and controls

x	*y*	*z*	Anatomic region	BA	Z
−40	−84	−8	Left inferior occipital gyrus	18	14.5
−28	−58	52	Left superior parietal lobule	7	7.57
−38	46	−6	Left middle frontal gyrus	10	6.78
−50	−34	16	Left superior temporal gyrus	29	6.07
−36	−2	58	Left middle frontal gyrus	6	5.14
14	−76	10	Right cuneus	17	14.8
30	−57	−13	Right fusiform gyrus	19	13.6
48	−66	−2	Right inferior temporal gyrus	37	10.6
38	−88	14	Right middle occipital gyrus	19	9.38
24	−64	52	Right superior parietal lobule	7	7.69

Stereotactic coordinates: *x,* left–right; *y,* anterior–posterior; *z,* inferior–superior distance in millimeters from the anterior commissure. Z-score denotes activation level; BA, Brodmann's area.

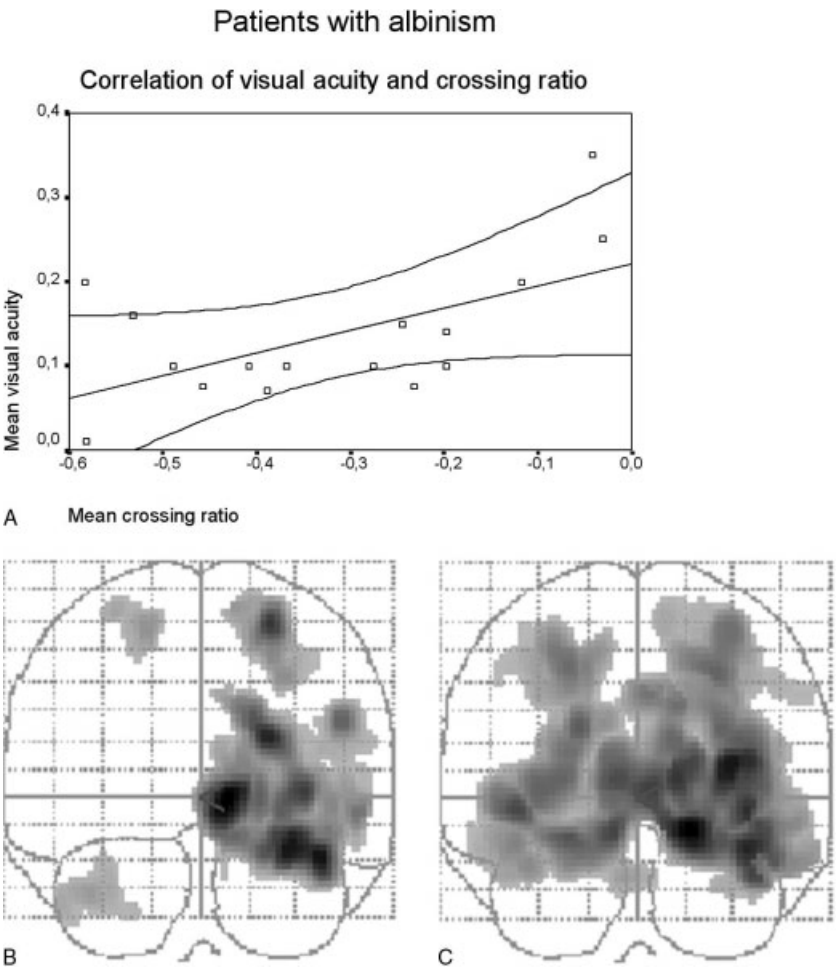

Figure 7.
Correlation of visual acuity and crossing ratio in albinos. **A:** Mean crossing ratio vs. mean visual acuity for the albinism group. There was a linear correlation (straight line) within the limits of low visual acuity given by the biological constraints of albinism. Curved lines indicate 99% confidence intervals. **B:** An example of left eye stimulation in one albino with low visual acuity and a high crossing ratio and corresponding almost exclusive activation of the contralateral hemisphere. **C:** An example of left eye stimulation in one albino with rather high visual acuity, a low crossing ratio and corresponding bilateral activations, although there remains a superiority of the right hemisphere due to predominant chiasmatic crossing.

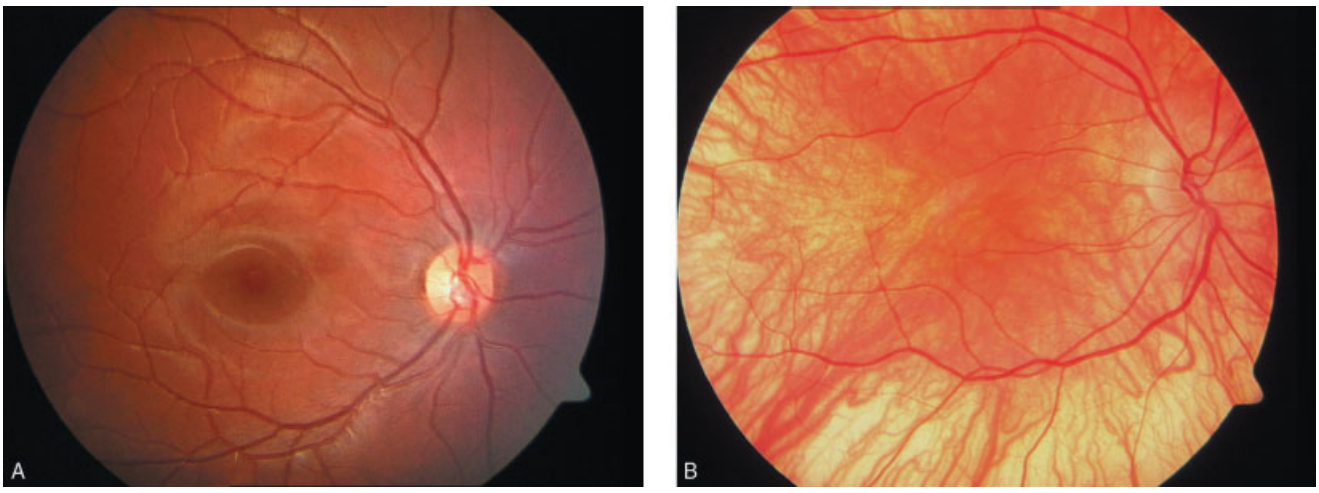

Figure 8.
Prototypical examples of fundus pictures. **A:** Normal control showing a regular optic nerve head and fovea. **B:** Patient with albinism demonstrating pronounced peripheral and central hypopigmentation as well as foveal and macular hypoplasia.

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