Identifying Human Albinism: A Comparison of VEP and fMRI

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Purpose. To compare VEP and fMRI as a means of detecting the abnormal visual projections in albinism in different stimulation conditions.

Methods. Cortical response to monocular full-field pattern-onset and hemifield pattern-onset and -reversal stimulation of 18 subjects with a known diagnosis of albinism, 17 control subjects, and 6 control subjects with infantile nystagmus syndrome (INS) was determined by VEP and fMRI. An asymmetry index was used to quantify the extent of response lateralization as measured by both VEP and fMRI. The extent to which each method and stimulus combination differentiated participant groups was summarized with a receiver operating characteristic (ROC) analysis, where $A_{A\text{-}C}$ and $A_{A\text{-}N}$ refer to areas under the ROC curve for albino versus control and albino versus nystagmus comparisons.

Results. Cortical response to full-field monocular stimulation conditions offered robust detection of the abnormal response lateralization in albinism, with fMRI ($A_{A\text{-}C} = 1.00$; $A_{A\text{-}N} = 0.91$) being slightly more robust than the VEP under these conditions ($A_{A\text{-}C} = 0.91$; $A_{A\text{-}N} = 0.79$). Hemifield stimulation paradigms were somewhat poorer at differentiating between groups, particularly when VEP was used in combination with pattern-reversal stimulation (pattern-onset fMRI $A_{A\text{-}C} = 0.94$, $A_{A\text{-}N} = 0.84$, and VEP $A_{A\text{-}C} = 0.86$, $A_{A\text{-}N} = 0.86$; pattern-reversal fMRI $A_{A\text{-}C} = 0.90$, $A_{A\text{-}N} = 0.88$, and VEP $A_{A\text{-}C} = 0.69$, $A_{A\text{-}N} = 0.64$). However, when only the most posterior aspects of the occipital lobe were considered with hemifield stimulation, fMRI achieved the best differentiation between the subject groups, most notably with hemifield pattern-reversal stimulation ($A_{A\text{-}C} = 1.00$; $A_{A\text{-}N} = 1.00$).

Conclusions. An interocular comparison between the lateralization of cortical responses elicited by full-field stimulation reliably distinguished between those with albinism and control groups, when both fMRI and VEP were used to assess cortical responses. Hemifield stimulation of one eye offers an alternative method for assessing misrouting associated with albinism and is highly effective when cortical signals are assessed with fMRI, but less so when VEP is used. (*Invest Ophthalmol Vis Sci.* 2008;49:238–249) DOI:10.1167/iovs.07-0458

Albinism is a genetic condition of hypopigmentation caused by an abnormality in melanin pigment production. The absence or reduction of melanin has a severe impact on the development of the eye and visual system, such that persons with albinism display a variety of ophthalmic deficits, including foveal hypoplasia, translucency of the iris, nystagmus, reduced visual acuity[1–3] and an abnormal decussation pattern at the optic chiasm.[4–8] The wide spectrum of pigmentation levels in albinism, in particular the near-normal hair and skin pigmentation levels in some types of albinism such as ocular albinism and oculocutaneous albinism type 2, can make diagnosis of albinism challenging in some individuals. Thus, phenotypic evaluation alone is seldom sufficient for definitive diagnosis, and additional diagnostic tests must be used.[9] Ophthalmic examination is routinely used to detect the presence of foveal hypoplasia; however, while this abnormality is present in all forms of albinism, it is not a retinal feature restricted to albinism and may be found in other disorders such as aniridia.[10] The characteristic, which is thought to distinguish albinism from other visual disorders resulting in foveal hypoplasia,[10] and other disorders of hypopigmentation,[11–13] is the abnormal routing of visual pathways from the eye to the brain. Clinically, it is this abnormality in conjunction with phenotypic evaluation and ophthalmic examination that has been used to diagnose albinism.[9]

Evoked potentials were first shown to detect the abnormal visual projection in individuals with albinism in a study by Creel et al.,[7] in which the albino subjects displayed a marked hemispheric lateralization of visual response to monocular full-field stimulation. Further studies confirmed these observations[8,14,15] although the consistency in detection of a lateralized response was variable. In two separate studies, Creel et al.[7,16] found the detection rate of a lateralized visual response in albinos by VEP was 70%, but other studies have reported lower detection rates.[17] By contrast, Apkarian et al.[8,18] and Apkarian and Shallo-Hoffmann[19] reported 100% detection rates in their studies. A summary of these and other VEP studies along with their lateralization detection rates are listed in Table 1.

The discrepancies in visual response lateralization as measured by VEP may in part be attributed to the stimulus type used to elicit the VEP. Creel et al.[25] examined the effect of stimulus type on the VEP and found that pattern-onset stimulation offered more robust results than pattern-reversal or flash-modulated stimulation. Similarly, Apkarian et al.[8,18] and Apkarian and Shallo-Hoffmann[19] found pattern onset to be the most effective stimulus for the detection of abnormalities indicative of albinism. Further problems with VEP diagnosis arise from confounding factors such as nystagmus. Despite the fact that nystagmus is known to affect VEP responses significantly [25–27] and is present to some degree in all individuals with albinism,[28] very few studies looking at the efficacy of the VEP in albinism diagnosis have included nystagmus control groups, to distinguish effects caused by nystagmus from those caused by the abnormal visual pathways.[19,23,24]

The underlying methodology used by all VEP studies employing full-field stimulation to detect the misrouting in albinism relies on a form of interocular comparison. In normal individuals, the distribution of scalp potentials in response to monocular stimulation shows wide variation across subjects, but the distribution remains unaltered within an individual

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TABLE 1. Previous Studies Testing the Efficacy of Diagnosis of Human Albinism by Using VEPs

Study	Stimulus	Albinos*	Controls*	Nystagmus*
Creel et al.[7]	Flash	14/20	10/10	—
Creel[16]	LO	50/72		
	PO	50/72	30/30	—
	PR	50/72		
Carroll et al.[14]	PR	14/15	—	—
Apkarian et al.[8]	PO	78/78	34/34	—
Apkarian et al.[18]	PO	96/96	44/44	—
Boylan et al.[15]	Flash	20/20	22/22	—
Russell-Eggitt et al.[20]	Flash	20/20	20/20	—
Apkarian and Shallo-Hoffmann[19]	PO	10/10	—	10/10
Bouzas et al.[17]	PO	14/31	9/9	—
Jarry et al.[21]	Flash	3/16	26/26	—
Soong et al.[22]	Flash	17/21	17/21	—
Dorey et al.[23]	PO	26/36†	27/27	2/3
	Flash	17/36†	11/11	3/3
Pott et al.[24]	PO	6/6	20/20	4/4
	Flash	6/6	15/20	3/4

Stimulus, full-field LO, luminance onset; PO, pattern onset; PR, pattern reversal.

* Fraction refers to the number of albino or control subjects with a response lateralization indicative of abnormal and normal visual pathways, respectively, over the total number studied.

† Only subjects showing some clinical features of albinism are included in this total.

when stimuli are presented to each eye in turn. In albinism, however, the distribution changes depending on the stimulated eye, thereby reflecting the abnormal visual projections characteristic of the condition. The reliance of the VEP test for albinism on an interocular comparison of responses can make it vulnerable to visual deficits that affect one eye only. In some cases, severe image degradation may prevent responses from being recorded from one eye. A retinal lesion affecting the hemiretina of one eye would also result in differing response lateralization for each eye. It would be useful, therefore, to develop a test that could capture the abnormality expressed in albinism by stimulating one eye only. Monocular stimulation can be achieved by independently stimulating the nasal and temporal retina of one eye, such that the abnormal routing from the temporal retina can be assessed. Initial attempts to investigate this by VEP were undertaken by Creel et al.[25] who demonstrated that stimulation of selective parts of the temporal retina in albino patients allows for a rough estimate of the extent of the abnormal projection. More recent work by Hoffmann et al.[29] supports these conclusions. Selective visual field stimulation or hemifield stimulation, however, has rarely been used in the detection of the abnormal albino decussation pattern,[14,21,30] possibly because of the often paradoxical lateralization patterns that have been reported in some instances.[31]

Although the VEP in response to full-field monocular stimulation has been the clinical standard for measuring cortical response lateralization in albinism, functional (f)MRI offers an alternative method for detecting cortical responses with greater spatial resolution. Studies have noted the ability of fMRI to detect a lateralized cortical response in albinism that is consistent with the abnormal visual projection[30,32,33]; however, there has been no study that compared the clinical standard of VEPs with fMRI in a group of subjects. Such a comparative study would allow the sensitivity and specificity of both techniques to be determined.

In the present study, we determined how well VEP and fMRI distinguish individuals with albinism from normally sighted individuals and from those with nystagmus by measuring lateralization of visual responses to full-field pattern-onset stimulation. We also presented pattern-onset and -reversal stimuli to the nasal and temporal retina of one eye in the same groups, to determine how those groups can be differentiated with fMRI and VEP for a monocular test.

MATERIALS AND METHODS

Eighteen subjects with albinism participated in the study. These subjects were either referred to us through an ophthalmologist or had responded to advertisements placed with the Nystagmus Network UK and the Albinism Fellowship UK. The albino subject group had a mean age of 42 years (range, 18–65) with 14 women. Seven albinos had a confirmed diagnosis of OCA type 1, two had confirmed diagnosis of OCA type 2, and one subject had OA. The remaining eight subjects with albinism were classified as OCA based on their pigmentation levels, but the exact subtype was unclear. All 18 subjects completed the fMRI study; however, two subjects did not complete the VEP component of the study. It is important to note that, although we were confident of the diagnosis in this group, we had no access to previous VEP or clinical evaluations of these patients. All the measurements reported herein were therefore performed as part of the study.

Six control subjects with infantile nystagmus syndrome (INS) with mean age of 33 years (range, 18–54), were also recruited to participate in the study (three women) via the Nystagmus Network UK. These subjects had no known diagnosis of albinism. We use the term infantile nystagmus syndrome (INS; as described in the CEMAS [Classification Of Eye Movement Abnormalities and Strabismus] report[34]) to describe our control patients with ocular instabilities. Although INS includes patients with latent components to their eye movements, we suspect that two of our patients, HR and MAS, may best be described as patients with fusion maldevelopment nystagmus syndrome (FMNS; see the CEMAS report). We used INS to describe the group as a whole, for simplicity. Visual acuities based on a Snellen eye chart and nystagmus amplitude, frequency, and foveation time,[35] assessed with electrooculography (EOG), were measured in all subjects with albinism or INS. In some of the patients we tested, the EOG traces were too noisy for a good assessment of slow-phase velocity, particularly at slow speeds $\sim$4 deg^{-1}. In those subjects in whom we were able to determine foveation time, there was a significant positive relationship between acuity and foveation time (albinos: $r = 0.51$, $df = 12$, $P < 0.05$, INS: $r = 0.78$, $df = 4$, $P < 0.05$). It is worth noting that noise in the EOG traces may have resulted in a slight overestimation of the foveation time in all our subjects. Details on the subjects with albinism or INS are included in Tables 2 and 3, respectively.

Seventeen control subjects (10 women) with no known ophthalmic deficits also participated in the study. The control subjects' mean age was 39 years, with ages ranging from 18 to 64 years. All control subjects had normal or corrected-to-normal visual acuities. All subjects

TABLE 2. Subjects with Albinism

Subject	Gender	Age (y)	Classification of Albinism	Visual Acuity		Nystagmus (±deg)	Freq (Hz)	Mean Foveation Time (ms)
				Left	Right			
AHa	F	38	OCA	0.25	0.25	3.2	3.2	—
ALM	F	34	OCA	0.10	0.10	6.0	4.7	59
AnC	F	34	OCA2	0.50	—	1.5*	—	—
BE	M	60	OCA	0.33	0.33	1.5	2.9	77
CE	F	47	OCA2	0.21	—	—*	—	—
CH	F	58	OCA1a	0.27	0.20	4.0	4.0	82
CLH	F	21	OCA1	0.10	0.10	5.0	3.1	42
DH	M	19	OCA1a	0.08	0.13	8.0	2.2	49
ES	F	32	OCA	0.50	0.40	1.5	5.5	67
FM	F	65	OCA1b	0.10	0.17	2.7	2.2	82
JK	F	25	OCA1	0.17	0.20	2.0	3.2	73
JM	M	34	OA	0.10	0.10	4.1	1.8	41
LS	F	34	OCA	0.17	0.30	4.5	3.1	78
MG	F	54	OCA1a	0.10	0.17	5.0	4.0	38
RMN	M	64	OCA	0.33	0.25	4.0	3.8	—
SU	F	52	OCA1a	0.12	0.06	1.8	3.0	46
TM	F	55	OCA	0.17	0.17	7.0	3.1	81
VP	F	35	OCA	<0.1	0.10	6.0	4.0	58

* Albino subjects AnC and CE did not complete the VEP portion of our study, and therefore there were no eye movement recordings. The nystagmus amplitude for subject AnC was taken from a previous study[36]; however, no note of frequency and foveation time was made in that study.

gave their informed written consent; the study complied with the tenets of the Declaration of Helsinki and was approved by the Royal Holloway Ethics Committee.

Stimulus

The visual stimulus consisted of a circular high-contrast checkerboard with seven concentric annuli, each with 24 checks extending to an eccentricity of ±15° from a central fixation cross. The checkerboard was scaled so that check size increased with larger eccentricities. The first annulus of checks had a check size of 1.35° increasing linearly to 2.55° in the most peripheral checks. The stimuli were created in commercial software (MatLab; The MathWorks, Natick MA) and presented by visual display software (MatVis; Neurometrics, Oakland CA). Each subject underwent full-field monocular pattern-onset stimulation for each eye, as well as monocular hemifield pattern-onset and pattern-reversal stimulation of the subject's dominant eye. The pattern-onset stimulation was presented as repeating blocks of 33 ms ON and 482 ms OFF. The pattern-reversal stimulus consisted of counterphase checks reversing at a frequency of 1 Hz. Because of local health and safety constraints limiting the amount of time a patient can remain in the scanner within one 24-hour period, we did not perform full-field monocular pattern-reversal stimulation.

VEP Recordings

VEPs were recorded with 5 Ag/Cl surface electrodes positioned posteriorly in a line placed 10% of the nasion–inion distance above the inion. The central Oz electrode was placed at the midline, with the other electrodes at lateral spacings of 4 and 8 cm to the left and right of the midline. These were referred to a linked-ears reference. A ground electrode was attached to the wrist. Electrode impedance was always below 20 kΩ and generally was between 3 and 10 kΩ. Stimuli were presented on a CRT display (contrast: 98%, mean luminance: 30 cd/m^2) as continuously repeating 400-ms trials, for a total of 200 trials. Recordings were amplified (Neuroscan, El Paso TX), filtered (1–100 Hz), and digitized at a sampling rate of 2000 Hz (Scan 4.0 software; Neuroscan, El Paso TX). After acquisition, the trial results were averaged and digitally filtered (0–40 Hz). Each averaged trial began 100 ms before stimulus onset, such that a sample trial ran from −100 to +300 ms with respect to the stimulus onset. Baseline for peak amplitude measurements was defined as the mean from 0 to 50 ms with respect to the stimulus event. Peak amplitudes for each recording were determined at the latency of the absolute maximum in the difference trace of electrodes 2 and 4, where electrode 2 is over the left hemisphere and electrode 4 is over the right hemisphere.

Functional Magnetic Resonance Imaging

All functional data were acquired on a magnetic resonance scanner (3T Trio; Siemens, Erlangen, Germany). The visual stimulus was projected onto a Perspex (duPont, Wilmington, DE) screen with a video projector located outside the scanner room (contrast: 99%, mean luminance: 1600 cd/m^2). The screen was placed in the bore of the scanner at the end closest to the subject's head, and a mirror mounted on the head

TABLE 3. Subjects with INS

Subject	Gender	Age (y)	Visual Acuity		Nystagmus (±deg)	Freq (Hz)	Mean Foveation Time (ms)
			Left	Right			
CA	M	35	0.67	0.67	1.8	4.0	54
GJ	M	33	0.33	0.67	3.0	3.9	74
GT	M	54	0.30	0.30	1.4	4.5	56
HR	F	31	0.25	<0.1	4.5	5.0	30
MAS	F	26	<0.1	0.10	3.5	2.5	45
MR	F	18	0.33	0.33	4.0	4.8	37

coil enabled the subject to view the projected stimulus. Subjects were provided with refraction, by means of MR compatible trial lenses, only if it improved their visual acuity.

The fMRI stimulus presentation occurred as a blocked design with 36-second epochs or cycles, each consisting of an 18-second stimulus presentation and 18-second uniform gray background, with a central fixation cross throughout. Each cycle was repeated seven times for a total experimental duration of 252 seconds.

T_2^* images were acquired throughout the stimulus presentation using a multislice gradient-echo EPI (echo–planar imaging) sequence (TE = 52 ms, TR = 3 s, 128 × 128 acquisition matrix, field of view 24 cm). A set of 16 coronal slices positioned over the back of the head ensured full coverage of the occipital lobe of both hemispheres. A total of 84 temporal samples were obtained.

In addition to the functional data, high-resolution MP-RAGE (magnetization-prepared rapid gradient-echo) image volumes were acquired for registration with the lower resolution EPI images and to facilitate anatomic signal localization. We acquired 176 sagittal slices to cover the whole brain, with an in-plane image matrix of 256 × 256 voxels, an in-plane resolution of 1.0156 × 1.0156 mm, and a slice thickness of 1.0 mm. The additional imaging parameters were as follows: TI = 1100 ms, and TE = 4.43 ms, TR = 11.14 ms, and flip angle = 8°, for a total acquisition time of 8 minutes and 21 seconds.

fMRI Data Processing

Postacquisition data were analyzed using Vista Software (courtesy of the Wandell Laboratory, Stanford University; http://white.stanford.edu). The first 12 of the 84 acquired functional data volumes were discarded to ensure that the magnetization had reached a steady state. The time series for every voxel in the remaining 72 volumes was determined and its correlation with the fundamental frequency of stimulation was calculated.

In-plane functional slices for each individual were aligned with the respective high-resolution T_1-weighted anatomic scan. The Talairach transformations to map the high-resolution anatomic scan for each subject into Talairach space[37] were determined by specifying a set of nine predetermined points, including the AC and PC points. A set of anatomically defined volumes to cover early visual areas based on Talairach coordinates were then transformed onto the subject's anatomic scan and from there, using the transformation determined through the alignment process, into the in-planes. These anatomic areas included the left and right inferior occipital lobes, the left and right cuneus, and the left and right lingual gyri. These areas covered an extensive part of the occipital lobe, ensuring inclusion of multiple visual areas. The regions of interest (ROIs) were then used to calculate the fMRI asymmetry index (A.I.).

Asymmetry Indices

An asymmetry index was defined for the VEP and fMRI measurements, to quantify the degree of response lateralization. The VEP asymmetry index was based on the study by Apkarian,[38] in which the peak response amplitude for each electrode is plotted as a function of electrode position and the surface area under electrodes 1 to 3 and electrodes 3 to 5 is used to define the asymmetry index as follows:

$$\text{for} \quad A_L > A_R, \quad \text{A.I.}_{\text{VEP}} = \left(\frac{A_R}{A_L}\right)$$
$$\text{else} \quad \text{A.I.}_{\text{VEP}} = 2 - \left(\frac{A_L}{A_R}\right) \qquad (1)$$

where A_L is the surface area under the left hemisphere electrodes (defined as the area bounded by the lines joining the amplitudes at electrodes 1, 2, and 3), and A_R is the surface area under the right hemisphere electrodes (defined as the area bounded by the lines joining the amplitudes at electrodes 3, 4, and 5).

An fMRI asymmetry index based on a Michelson contrast ratio, but normalized for ROI size, was defined to quantify the degree of response lateralization for the fMRI data as follows:

$$\text{A.I.}_{\text{fMRI}} = \frac{N_L N_{RT} - N_R N_{LT}}{N_L N_{RT} + N_R N_{LT}} \qquad (2)$$

where N_L and N_R are the number of significant voxels at a given correlation threshold in the left and right hemisphere ROIs, and N_{LT} and N_{RT} are the total number of voxels in the respective ROIs. The asymmetry index therefore ranges from −1 to +1, where a value of 0 indicates equal distribution of signal across both hemispheres, −1 indicates a response lateralized to the right hemisphere, and +1 a response lateralized to the left hemisphere. The asymmetry index was calculated for correlation coefficients from 0 to 0.5 but, for comparison with the VEPs, a correlation threshold of 0.30 (corresponding to $P < 0.01$) was used.

Results

Full-Field Stimulation

Figure 1 depicts the VEP response in a subject with INS and a subject with albinism during full-field pattern-onset monocular stimulation of the left and right eyes. In the INS subject, the cortical response recorded from an electrode at one location remained unchanged regardless of which eye was stimulated (Fig. 1A). This resulted in remarkably similar response lateralization patterns across the head for stimulation of each eye (Fig. 1C). The VEP response in the subject with albinism, however, was different (Figs. 1B, 1D). There was a distinct lateralization of the cortical response wherein the greatest signal was recorded from the electrodes located over the hemisphere contralateral to the stimulated eye. This response is consistent with the abnormal visual pathway routing in albinism: Since a large proportion of temporal retinal fibers project to the contralateral hemisphere together with nasal retinal fibers, the input from each eye is processed predominantly by the contralateral hemisphere. As a result, the cortical response to full-field stimulation is dependent on, and contralateral to, the stimulated eye.

The cortical lateralization in response to full-field monocular stimulation as detected by fMRI is evidenced in Figure 2. In the left column, voxels whose response profiles correlated significantly with the fundamental frequency of stimulation ($P < 0.01$) are overlaid on the individual's reconstructed cortical surface for a control subject (Fig. 2A), an INS subject (Fig. 2B), and an albino subject (Fig. 2C). In the control and the INS subjects, the activation was distributed bilaterally regardless of the stimulated eye. In the subject with albinism, however, there is a distinct lateralization of cortical response such that activation is dominant in the hemisphere contralateral to the stimulated eye.

The response lateralization in subjects is quantified by means of the fMRI asymmetry index, which is plotted for these three subjects as a function of the correlation threshold of the voxels (Fig. 2, right column). Thus, the plots depict the extent of response lateralization for increasingly stringent statistical thresholds. In the control and the INS subjects, the asymmetry indices as a function of correlation threshold were similar regardless of the eye stimulated and showed remarkably little hemispheric lateralization of visual response. The albino subject, however, showed a distinct lateralization of cortical response that was dependent on the eye stimulated, such that a greater response was always found in the contralateral hemisphere.

Because the detection of lateralization by full-field monocular stimulation depends on an interocular comparison, a sin-

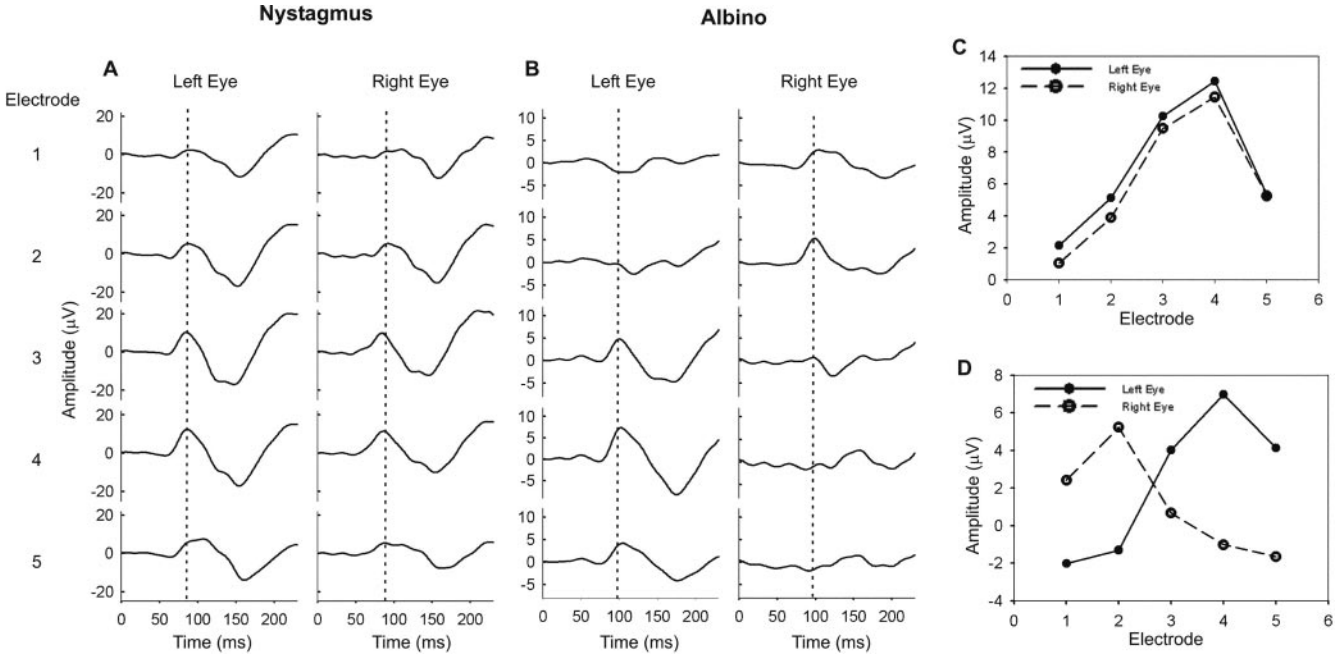

FIGURE 1. VEP recordings in an INS (**A**) and an albino (**B**) subject in response to monocular left and right eye full-field pattern-onset stimulation. Recordings for each electrode placed across the occiput are displayed from left hemisphere (electrode 1) to right hemisphere (electrode 5). *Vertical dotted line*: the time at which the peak amplitude measurements were made. The peak amplitudes as a function of electrode position for the left and right eyes are plotted in (**C**) and (**D**) for the INS subject and the albino, respectively.

gle measure is used to combine lateralization information from each eye for both VEP and fMRI. Clinical diagnostic testing for albinism based on VEP recordings has been investigated extensively by Apkarian and Shallo-Hoffmann[19] and Apkarian.[38] In their studies, an interocular asymmetry index (defined as the asymmetry index in response to left eye stimulation subtracted from the asymmetry index for right eye stimulation) was used as a measure to distinguish control from albino subjects, where values greater than 0.7 were been reported to indicate significant interocular asymmetry and thus an affirmative diagnosis of albinism. The same analysis was applied herein to test the efficacy of distinguishing the albino and control groups by VEP. We also defined an fMRI interocular index as the difference of the left and right eye asymmetry indices. However, as the range of asymmetry indices obtained by fMRI is different from those obtained by VEP, the Apkarian threshold of 0.7 is not applicable to fMRI data. Figure 3 displays the results of the VEP and fMRI interocular analyses. For the VEP recordings, one of the subjects with albinism had an interocular asymmetry of less than 0.7, the diagnostic threshold for albinism.[19,38] In addition, three subjects with INS had an interocular asymmetry greater than 0.7, as did one control subject. For our distribution of interocular VEP asymmetry indices, we can establish a cutoff to differentiate best between groups. The optimal value lies between 0.71 and 0.99, the lower value of this range being little different from Apkarian's.

The fMRI interocular index appeared better at segregating the control group from the albino group, with all control subjects displaying interocular asymmetries below 0.1 and all albinos having asymmetry indices above 0.1. Two INS subjects, however, still lie within the albino interocular index range. It is of note that the subjects with nystagmus who were misclassified herein had large acuity asymmetries and had particularly poor acuity in one eye, suggesting that an interocular comparison may be an inappropriate measure for detecting lateralization in such individuals, particularly as these individuals were also misclassified by VEP.

Hemifield Stimulation

The VEP response distribution to monocular hemifield pattern-onset stimulation is shown in Figure 4A. When nasal retina is stimulated in the control subjects, the response is lateralized to the contralateral hemisphere. Conversely, for stimulation of temporal retina, the response lateralization is ipsilateral. In the albino subject, however, the cortical response is lateralized to the contralateral hemisphere, regardless of the hemifield stimulated, reflecting the abnormal contralateral projection from the temporal retina.

The VEP response to hemifield pattern-reversal stimulation was similar to the pattern-onset response in the control group; however, both the INS control and the albino subjects had very small amplitude responses and indistinguishable lateralization patterns (data not shown). This finding agrees with previous research that has shown that nystagmus severely affects the VEP response to pattern-reversal stimulation.[25–27]

Figure 4B depicts the fMRI asymmetry index as a function of voxel correlation threshold in the same three subjects as in Figure 4A in response to nasal and temporal retina pattern-onset stimulation (results for pattern reversal were similar, data not shown). In the control and the INS subjects, cortical response was lateralized to the contralateral hemisphere for nasal retina stimulation and the ipsilateral hemisphere for temporal retina stimulation. As shown by VEP, the subject with albinism displayed contralateral lateralization, regardless of the hemifield stimulated.

Similar to the full-field analysis, we used a single measure to combine the lateralization properties in response to the stimulation of nasal and temporal retina. Since only one eye was stimulated for the hemifield experiments, the interocular index used in the full-field analysis was inappropriate and instead we defined an interhemifield asymmetry index, given by the *sum* of the asymmetry indices in response to nasal and temporal retina stimulation. Figure 5 displays the interhemifield indices for VEP and fMRI hemifield stimulation. It is apparent in Figure

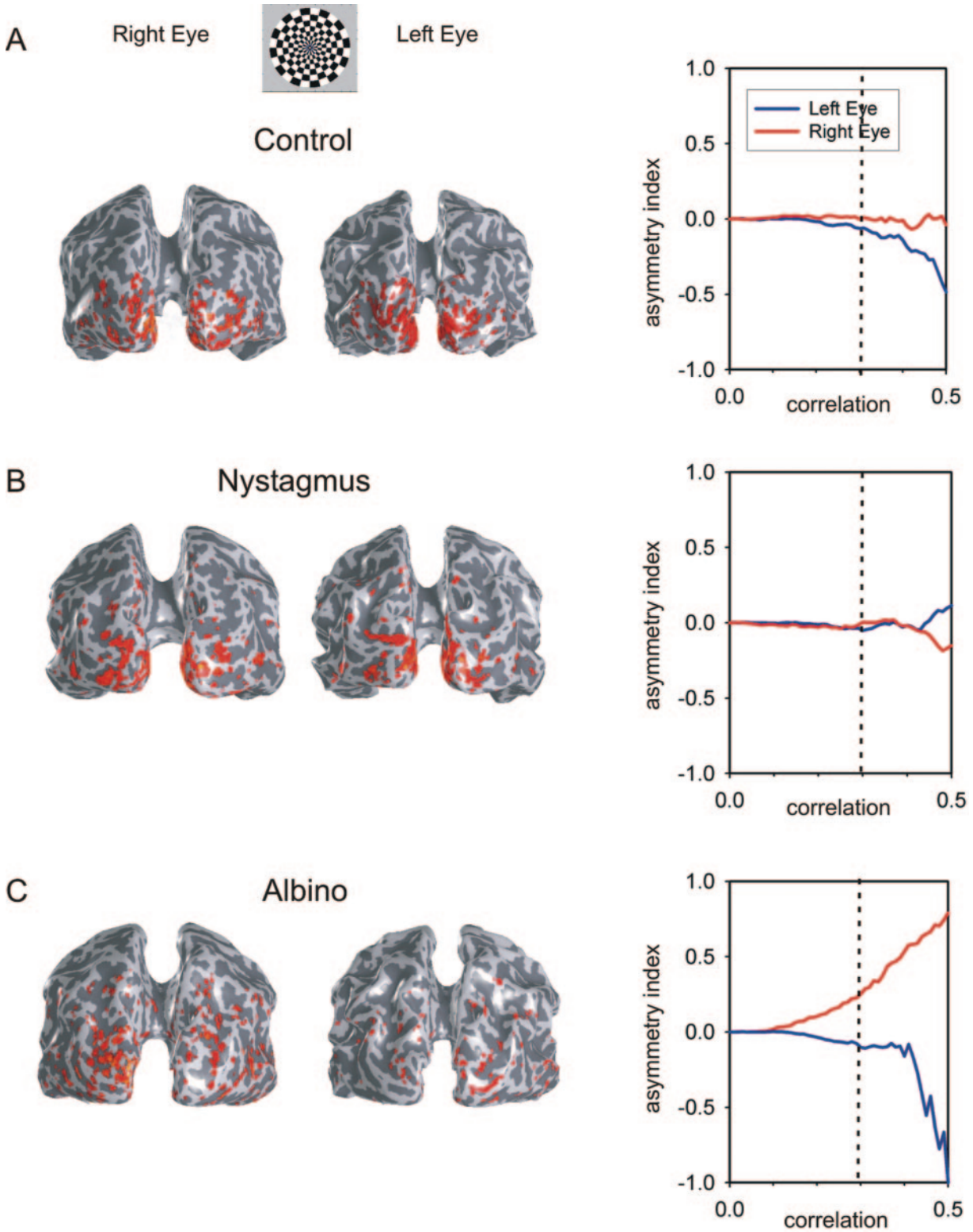

FIGURE 2. The cortical response to full-field pattern-onset stimulation for each eye as measured by fMRI is shown overlaid on a control (**A**), a nystagmus (**B**), and an albino subject's (**C**) cortical surface at a correlation threshold of 0.3. fMRI asymmetry indices for these subjects are plotted in the *right column*. The asymmetry index is plotted as a function of the correlation threshold of the cortical response, where c = 0.3 corresponds to $P < 0.01$. A positive asymmetry index reflects left hemisphere lateralization, and a negative asymmetry index reflects right hemisphere lateralization. Only the subject with albinism displayed a marked lateralization of visual response to full-field stimulation.

5A that the VEP interhemifield asymmetry indices in response to pattern-onset and particularly to pattern-reversal stimulation were unable to distinguish accurately the control groups from the albino groups. The fMRI interhemifield asymmetry indices for hemifield stimulation (Fig. 5B) appeared better than VEP measures at differentiating the subject groups. However, over-

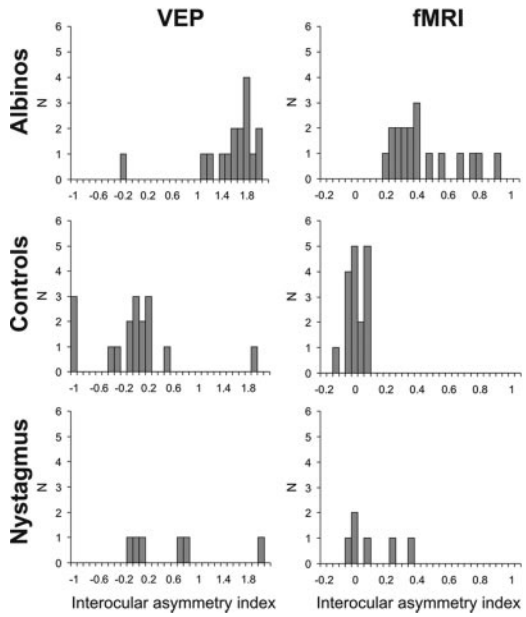

FIGURE 3. Histograms of the interocular asymmetry indices in response to full-field pattern-onset stimulation for each subject group as measured by VEP and fMRI. The interocular asymmetry index is calculated as the asymmetry index of the right eye minus that of the left eye.

all, the hemifield approach appeared to be poorer than our full-field measurements at distinguishing the control and albino groups.

Is it possible to refine our hemifield analysis to differentiate better between the groups? Because individuals with albinism vary in the extent to which temporal retinal fibers project contralaterally,[25,29,36,39] the abnormal contralateral projection from temporal retina may be quite small in some individuals. In such cases, there may be a significant contribution to the cortical response from the ipsilateral projections arising in the peripheral temporal retina, which could result in an asymmetry index similar to a normal individual. To assess the extent of the abnormal projection and thus the relative contribution from each hemisphere to the asymmetry index, we evaluated the hemispheric asymmetry for our fMRI data in successive acquisition slices from posterior to anterior aspects of the occipital lobe. For this analysis, slice 1 for all subjects was normalized to be the first slice containing a part of the predefined ROI.

Figure 6 plots the asymmetry index as a function of coronal slice number from posterior to anterior cortex in response to pattern-reversal stimulation of the nasal and temporal retina (similar results were obtained for the pattern-onset hemifield, data not shown). The top panels depict the subset of subjects with albinism whose interhemifield asymmetry was indistinguishable from that in the control subjects, and the remainder of the albino subjects are plotted in the bottom two panels. These plots have been normalized for the individuals' stimulated eye and hemifield, such that a positive asymmetry index indicates contralateral lateralization and a negative asymmetry index an ipsilateral response lateralization. When nasal retina was stimulated, all albino subjects exhibited contralateral lateralization of cortical response across all slices, similar to the control groups. When the temporal retina was stimulated, the albino subjects with a distinct interhemifield response (Fig. 6, bottom right panel) also displayed a predominantly contralateral response lateralization that became less pronounced in the more anterior slices (higher slice number), unlike the control group's response to temporal retina stimulation, which remained ipsilateral throughout the posterior to the anterior cortex. The subjects with albinism whose interhemifield asymmetry was indistinguishable from the control group's however (Fig. 6, top right) had a larger contralateral response only in very posterior slices and reverted to the normal ipsilateral lateralization pattern exhibited by the control groups in the more anterior slices. They thus had a smaller abnormal projection arising from temporal retina. When the asymmetry index was averaged over all acquired slices, as was the case for the interhemifield asymmetry analysis, the relative contribution from the normal temporal retina ipsilateral projection was such that these subjects' interhemifield asymmetry became indistinguishable from the control group's. Thus, to overcome the confounding contribution from normal ipsilateral temporal retina projections in the albino group, the hemifield analysis must be weighted to posterior slices, where central visual field representations are found.

We therefore performed an additional analysis of interhemifield asymmetry which incorporated only the asymmetry index from the most posterior slice (slice 1). In this way, we isolated activity from central visual field locations that, in albinism, consistently exhibit an abnormal projection to the contralateral hemisphere in response to temporal retina stimulation (see Fig.

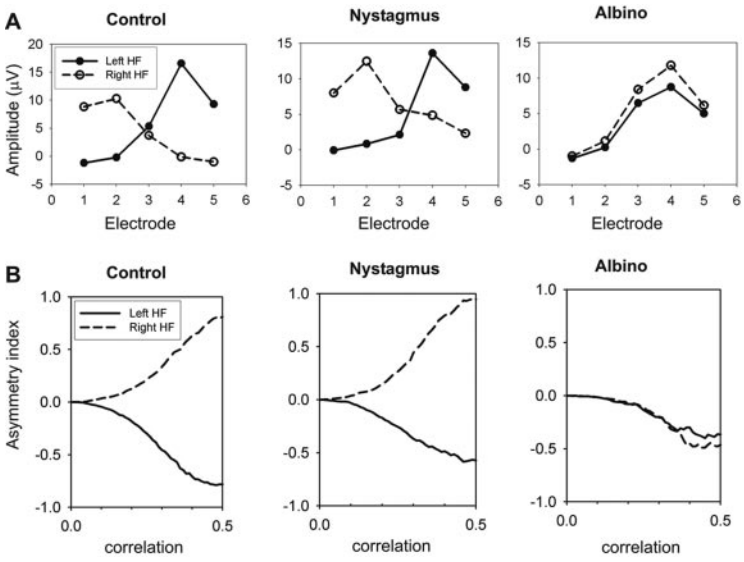

FIGURE 4. Cortical response lateralization in response to hemifield pattern-onset stimulation of the left eye in one control, one INS, and one albino subject. In (**A**), peak amplitudes as measured by VEP are plotted across electrodes from left hemisphere (electrode 1) to right hemisphere (electrode 5). In (**B**), asymmetry index as measured by fMRI is plotted as a function of cortical response correlation threshold. In both control groups, the response to hemifield stimulation was lateralized to the hemisphere contralateral to the stimulated hemifield, whereas the albino displayed a response lateralized to the hemisphere contralateral to the stimulated eye.

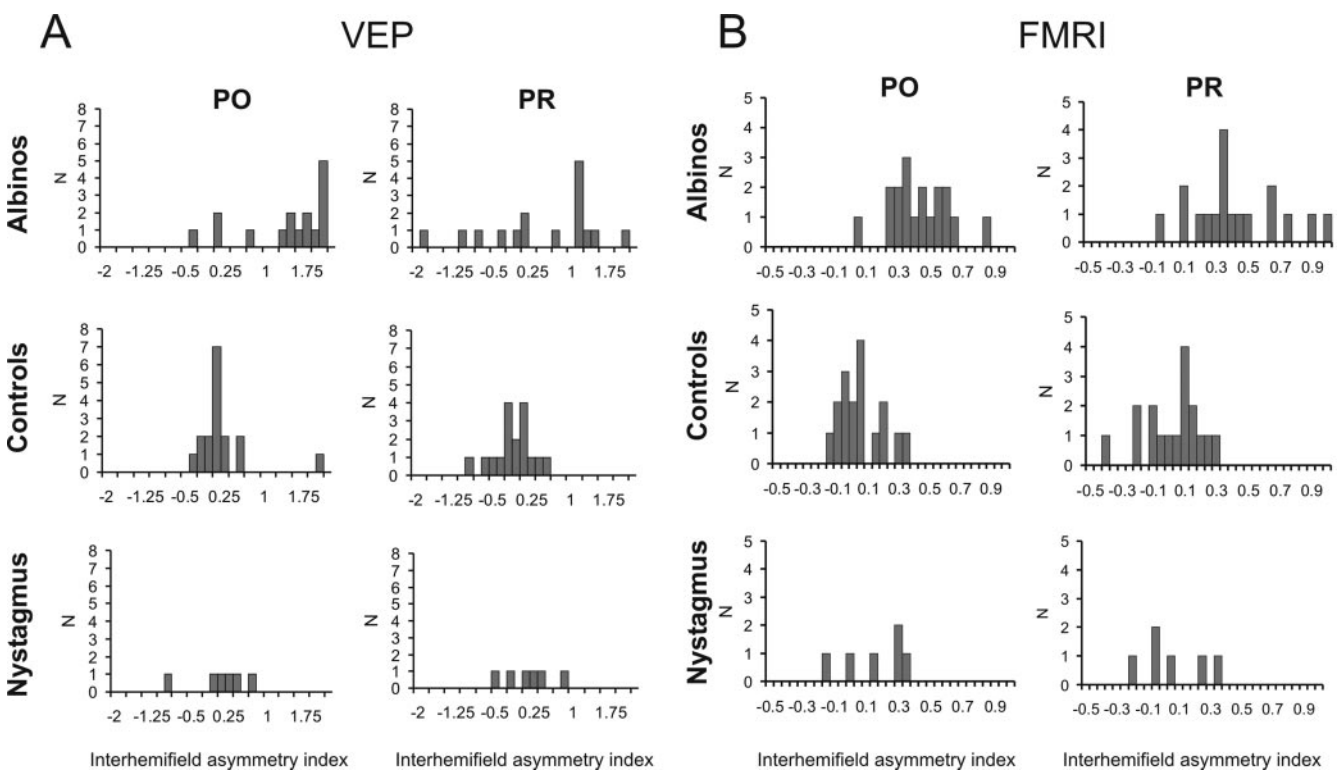

FIGURE 5. Histograms of the interhemifield asymmetry indices across subject groups for hemifield pattern-onset and -reversal stimulation as measured by VEP (**A**) and fMRI (**B**).

6). Figure 7 shows the results of the analysis. There are clear differences between the sample distributions of interhemifield asymmetry, depending on whether the pattern-onset or -reversal stimulation procedure was used. For pattern-onset stimulation there was considerable overlap between the groups, but this disappeared when pattern-reversal stimulation was used.

ROC Analysis

To assess the relative efficacy of the different stimulation paradigms at distinguishing the albino and control groups, we calculated the receiver operating characteristic (ROC) curve for each set of analyses. Figure 8 depicts the area under the ROC curve for the different stimulation paradigms and analysis methods as a function of correlation threshold. As correlation increased, the area under the ROC curves reached a plateau and in most cases began to decrease at correlations between 0.4 and 0.5. At these higher correlation thresholds, the number of voxels included in the asymmetry index calculation decreases, making the asymmetry index less reliable, and correspondingly decreases the differentiability between subject groups. Above a correlation of 0.5, some subjects yielded no active voxels, which means the ROC analysis would no longer be appropriate because the membership of the groups would change in size. Our choice of using 0.3 as a correlation threshold for the data just presented and ROC analysis was based on several points. First, the threshold selects highly significant activations ($P < 0.01$). Second the plots in Figure 8 reveal that a threshold of 0.3 is very close to the center of the plateau, meaning that the segregation of groups is very stable around 0.3.

Table 4 lists the area under the ROC curves at a correlation of 0.3. It is clear that full-field pattern-onset stimulation provides an excellent means by which individuals with albinism can be differentiated from control subjects, regardless of whether VEP or fMRI is used to measure the cortical response. However, both techniques are not as successful at differentiating individuals with albinism from subjects with INS. The hemifield stimulation protocol is successful at highlighting the abnormal projection associated with albinism, particularly when fMRI responses are considered, demonstrating that it is possible to use a monocular test. However, a simple hemifield protocol alone is not as good as the interocular comparison of response to full-field stimulation for

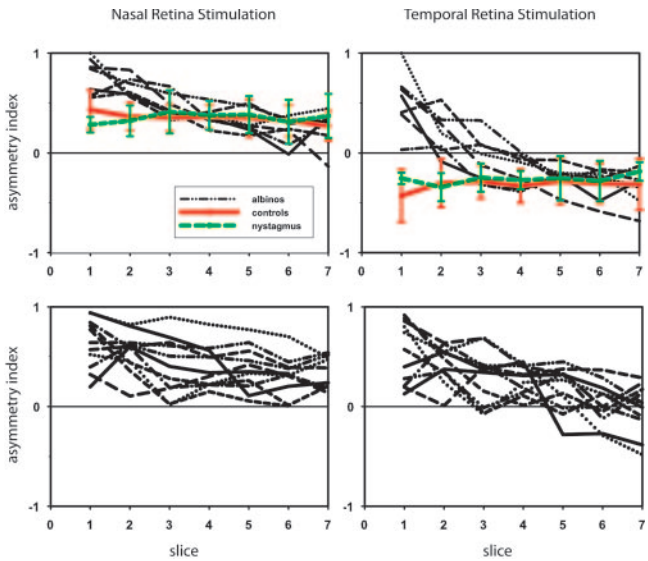

FIGURE 6. fMRI asymmetry indices as a function of coronal slice number plotted from posterior to anterior cortex (increasing slice numbers) in response to nasal and temporal retina stimulation. *Top*: subjects with albinism whose interhemifield asymmetry index was indistinguishable from the control subject groups; *bottom*: the remaining albinos.

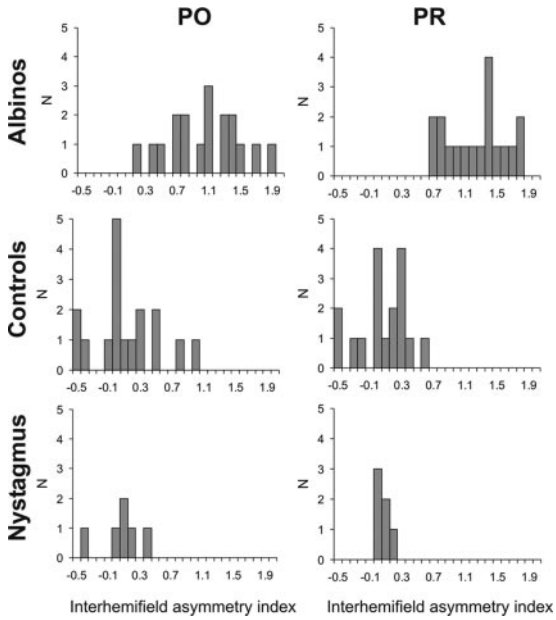

FIGURE 7. Histograms of interhemifield asymmetry indices across subject groups in response to pattern-onset and -reversal stimulation calculated using asymmetry indices for the most posterior fMRI acquisition slice only (slice 1).

both VEP and fMRI measurements. The advantage of fMRI is that responses can be assessed in restricted cortical locations that normally represent the central visual field. Previous research from our laboratory has shown that the two most posterior slices capture visual field mappings within 2° of the visual angle.[39] Thus, when analysis is weighted to central visual field representations by incorporating asymmetry information from posterior occipital lobe only, the interhemifield responses can be improved markedly to the extent that they outperform the full-field measurements. Under these circumstances, the interhemifield comparison based on pattern-reversal hemifield stimulation arrives at perfect differentiation between participants from all groups.

Given the success of the single slice analysis for the hemifield stimuli, we also thought it would be useful to apply this method to a full-field experiment to determine whether a single measurement made from one eye only, by incorporating information from both nasal and temporal retina, would provide a sufficient means of differentiating between groups. The results indicate that a single-slice analysis in response to a monocular full-field stimulus applied to one eye only was insufficient to distinguish a normal visual response from an albino visual response, largely because control subjects with normal visual pathways can display an intrinsic lateralization of their cortical response to full-field stimulation, and it is only by comparison with the response from the other eye that the lateralization is shown to be independent of which eye is stimulated. Thus, a reliable detection mechanism of the lateralized visual response indicative of albinism must consist of either an interocular or an interhemifield comparison.

DISCUSSION

The results shown herein indicate that fMRI in response to monocular full-field pattern-onset stimulation was able to detect a lateralized visual response, indicative of abnormal visual pathways, in all subjects with albinism. Furthermore, all control subjects, with the exception of two subjects with nystagmus, had a response asymmetry that was distinct from the albino response. By contrast, VEPs detected a lateralized visual response in 15 of 16 albino subjects. In addition, one control subject and three INS subjects had a VEP response asymmetry that was indistinguishable from the albino lateralization pattern.

Previous work by Apkarian and Shallo-Hoffmann[19] and Apkarian[38] suggest a VEP interocular asymmetry index of 0.7 or greater is indicative of albinism. In the results presented herein, a threshold of 0.7 for the VEP was insufficient to distinguish completely the control group VEP responses from the albino responses. Shifting this threshold did not result in a more accurate distinction of these two subject groups. In addition, several subjects with nystagmus had an interocular asymmetry index of 0.7 or higher, effectively classifying them as albino. Although our VEP results do not perfectly differentiate between groups as Apkarian et al.[8,18] have reported, our study reflects similar performance and indicates that their methodology yields very good results in the context of results derived by others (reviewed in Table 1).

A thresholding approach similar to the VEP interocular index was used to distinguish the albino and control response measured by fMRI: An interocular fMRI asymmetry of 0.1 or higher was found in all subjects with albinism. Of the six INS subjects, two had interocular asymmetries which fell within the albino range above 0.1. Despite the difference in the range of asymmetry index values for VEP and fMRI, it is clear from these data that an interocular asymmetry index with a modified threshold can be applied to analyze fMRI data in response to full-field monocular stimulation and can distinguish an albino response from a control response at least as, if not more, successfully than similar methodology by VEP.

Although both VEP and fMRI were good at differentiating a control response from an albino response and vice versa in response to full-field monocular stimulation, both techniques had difficulty in distinguishing the INS control group subjects' from the albino subjects' response. Similar false positives have been reported in previous VEP studies. Meienburg et al.[40] reported albino-like response lateralization in two patients with nystagmus with flash VEP, Dorey et al.[23] found one of three patients with nystagmus had albino-like lateralization for pattern onset, and Pott et al.[24] found one of four patients with nystagmus had albino-like lateralization for flash VEP. In the data shown, two INS subjects had an fMRI interocular asymmetry in the same range as albinos and three of the six INS controls had a VEP response that was indistinguishable from the albino response. In addition, the same two subjects who were misclassified by fMRI were also among the three misclassified by VEP. It is interesting to note that the subjects with nystagmus who were misclassified by VEP and fMRI interocular asymmetry indices had large acuity asymmetries, in particular two of the three subjects had very poor acuities in one eye. These results suggest that an interocular comparison may be an inadequate measure of cortical response lateralization in these subjects.

In patients with such significant visual impairment in one eye, be it the result of a retinal lesion or very poor acuity, an adequate visual response may not be obtained from the deficient eye. In these cases, a monocular test for albinism may be useful in detecting evidence of the misrouting in albinism. We have shown that monocular stimulation of nasal and temporal retina independently provides an alternative means of assessing the abnormal visual pathways present in albinism. By defining an interhemispheric asymmetry measure based on hemifield stimulation results, we were able to discern with slightly poorer capability, in the first instance, the different subject groups compared with the full-field monocular test. However, when the fMRI analysis was restricted to activation in only the most posterior acquisition slice, the differentiability of the subject groups improved markedly, so that the pattern-reversal

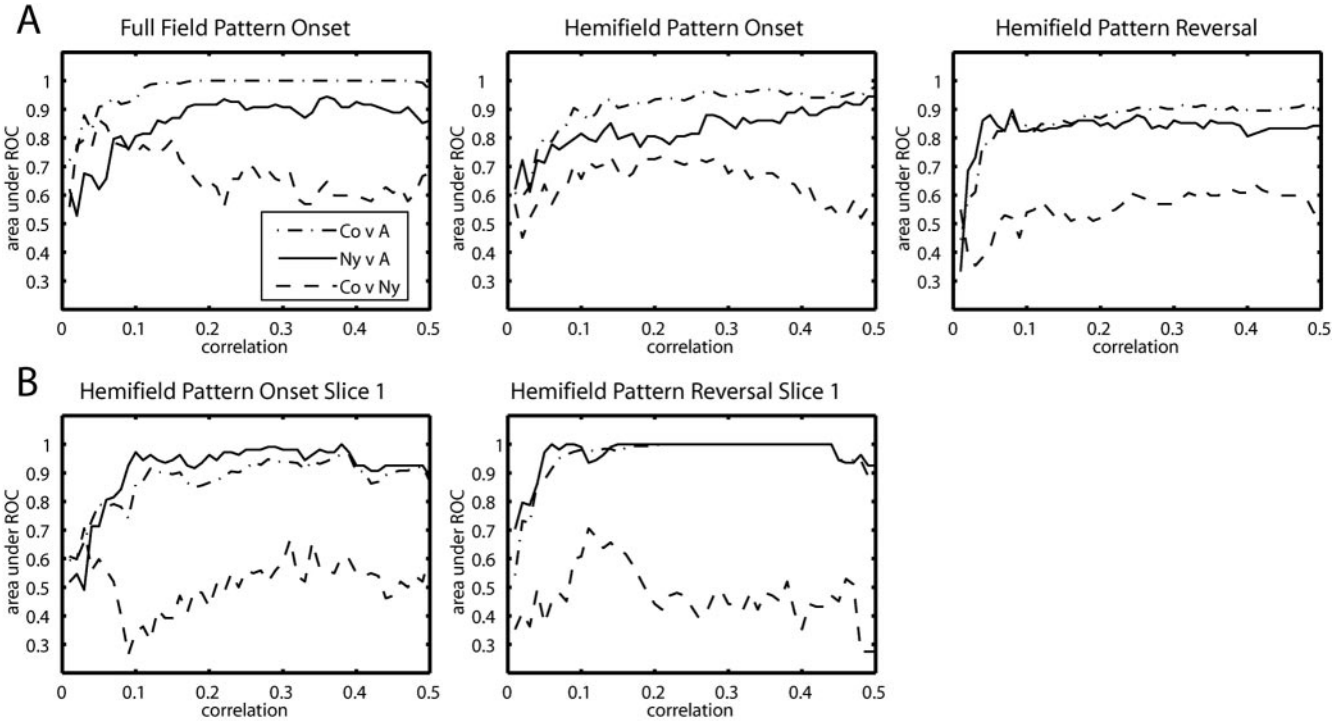

FIGURE 8. Area under the ROC curve as a function of correlation value in control versus albino, controls versus nystagmus, and nystagmus versus albino subjects for (**A**) full-field pattern-onset stimulation, hemifield pattern-onset stimulation, and hemifield pattern-reversal stimulation, and (**B**) the single-slice analysis hemifield pattern-onset and -reversal stimulation.

hemifield analysis outperformed even the analysis of the data derived from full-field stimulation. In addition, the spatially restricted hemifield analysis was successful in distinguishing the INS subjects who problematically fell within the albino asymmetry range in both the VEP and fMRI full-field analyses. These subjects displayed lateralization responses that fell well within the range of the other INS subjects for both the simple hemifield analysis and the more spatially specific single-slice analysis, clearly suggesting that a monocular test is more appropriate for assessing lateralization in these cases.

Our hemifield stimulation procedures were undertaken with two stimulus types. For fMRI the pattern-reversal and -onset stimulation procedures yielded similar results, when the occipital cortex was analyzed as a whole. When the most posterior slice only was considered, the data acquired during pattern-reversal stimulation better distinguished between participant groups than the data obtained during pattern-onset stimulation. VEP results were more strongly affected by the type of visual stimulation used. Recorded responses in all subjects with nystagmus (both control INS subjects and albinos) for the pattern-reversal stimulation paradigm were very poor. This effect of nystagmus on pattern reversal has been noted in previous studies[25–27] and emphasizes the importance of an appropriate stimulus selection for the VEP. A survey of past VEP studies of albinism, as listed in Table 1, indicates that the most effective diagnoses are obtained with the pattern-onset stimulation paradigm. In our study, however, nystagmus did not affect fMRI results to a similar extent. It should also be noted that in this study the rate of presentation of onset and reversal stimuli was taken from the VEP literature and it might be expected that fMRI approaches could be further improved by using pattern reversal at higher rates that normally elicit stronger activations from the visual cortex. This question is a topic for further research.

TABLE 4. Receiver Operating Characteristic Curve Area in Various Stimulation Conditions

	Control vs. Albino	Nystagmus vs. Albino	Control vs. Nystagmus
Full-field			
PO fMRI	1	0.9074	0.6569
PO VEP	0.9081	0.7917	0.7451
Hemifield			
PO fMRI	0.9412	0.8426	0.6373
PO VEP	0.8566	0.8646	0.5784
PR fMRI	0.9020	0.8796	0.5098
PR VEP	0.6949	0.6354	0.6569
Hemifield (slice 1 only)			
PO fMRI	0.9314	0.9815	0.5294
PR fMRI	1	1	0.4608

This is the first group comparison of the VEP and fMRI modalities and their sensitivity in detecting the abnormal visual pathway in albinism. Given the results presented, it is clear that both fMRI and VEP are capable of providing an assessment of the abnormal visual projections present in albinism. Although both techniques provided a means of detecting lateralization, it is important to note that they did not confer identical information about visual responses. There was little correlation between the fMRI asymmetry indices and those obtained by VEP (r = 0.28 for full-field stimulation; r = 0.28 and 0.07 for pattern-onset and -reversal hemifield stimulation, respectively). One reason for this poor correspondence of measures becomes clear in the fMRI hemifield analyses we performed, which incorporated information from the most posterior acquisition slice only. When the cortical response was restricted to central visual field representations that are always affected in albinism,[25,29,36] the differentiability of the groups improved. Thus, the success of the VEP and its primary difference from

fMRI may be its sensitivity to neuronal responses at, or close to, the cortical surface, since these generators are the largest contributors to the recorded VEP. By contrast, the additional information or signal provided from the more anterior cortical regions, as measured by fMRI, may not always confer advantages, as evidenced in the hemifield analysis.

It is clear from the results that both techniques have their relative advantages. Although the clinical use of VEP is likely to prevail in many instances because of its simplicity and low cost, fMRI offers a useful alternative for detecting the misrouting associated with albinism in cases in which the VEP results are ambiguous. In particular, fMRI can be useful in cases of patient referrals in which relatively few clinical symptoms of albinism are present. Such situations cause difficulties for VEP diagnosis, as shown in an extensive study by Dorey et al.,[23] who examined the correlation of clinical symptoms of albinism with electrophysiological abnormalities. In their study, a wide spectrum of subjects, some of whom displayed few or none of the clinical symptoms associated with albinism and some of whom had severe hypopigmentation and visual deficits, were studied by VEP. Subjects with a greater number or greater severity of clinical symptoms were more likely to have significantly abnormal VEP recordings. Similar correlations between albino characteristics and fMRI measures have also been observed. Schmitz et al.[33] showed an increase in cortical response lateralization with increased iris translucency and previous research from our laboratory has shown that higher pigmentation levels are associated with a less severe extent of misrouting.[39] However, even at high pigmentation levels where the extent of misrouting is smaller, the abnormality is significant and easily detected by fMRI. Thus, fMRI may be useful in subjects with fewer clinical symptoms of albinism due to its higher sensitivity. Furthermore, response asymmetry in the amplitude of the VEP has been reported in individuals with congenital stationary night blindness[41,42] and is therefore not, as previously believed, a signature VEP response found only in individuals with albinism. It is worth noting, however, that although *amplitude* asymmetry in the VEP cannot always reliably be detected and may not be a feature restricted to albinism, Dorey et al.[23] found that an interhemispheric *latency* asymmetry was more consistently present in individuals with albinism and more significantly correlated with their clinical features. Thus, additional information about the evoked response may improve the diagnostic capability of the VEP.

Finally, it is important to emphasize that the diagnosis of albinism is not based solely on the detection of abnormal visual pathways but is also contingent on a full ophthalmic examination. In the future, genetic testing may also play a more important role in diagnosis, as at least five different genes have been identified that can give rise to albinism.[43–48] Genetic research into albinism is ongoing and may identify involvement of further genes; however, the discovery of new genotypes is dictated largely by our ability to identify albino phenotypes. As a result, successful detection of albino misrouting is currently still a critical component in the diagnostic battery. As discussed previously, the detection of albino misrouting is affected by several factors, including nystagmus, the severity of other clinical symptoms, and/or acute loss of vision in one eye which would make an interocular comparison impossible. Therefore, the most appropriate measure of albino misrouting will be largely informed by the outcome of the individual's ophthalmic examination.

Conclusion

Our study largely reinforces the findings of Apkarian and Shallo-Hoffmann[19] and Apkarian[38] that interocular asymmetry of VEP responses provides a robust way of detecting the misrouting of visual fibers associated with albinism. Our findings also indicate that fMRI is equally good, if not better, at detecting this misrouting by using interocular comparisons. Further investigation of hemifield responses indicated that, particularly with fMRI, misrouting could be detected reliably but not perfectly. Assessment of fMRI misrouting in the most posterior aspects of the occipital lobe, however, allowed the participant groups to be distinguished perfectly and also provides an explanation of the success of the VEP in detecting misrouting, since its recorded responses are weighted to signals proximal to surface electrodes.

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