SHORT REPORT

Abnormal visual projection in a human albino studied with functional magnetic resonance imaging and visual evoked potentials

A B Morland, M B Hoffmann, M Neveu, G E Holder

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The albino visual pathway is abnormal in that many fibres from the temporal retina project to the contralateral visual cortex. The visual projections in a human albino and a control have been investigated with fMRI and VEP during independent visual stimulation of both hemifields. Activity in the occipital cortex in the normal was contralateral to the stimulated visual field, whereas it was contralateral to the stimulated eye in the albino, independent of the stimulated visual field. Thus, the albino visual cortex is activated not only by stimulation in the contralateral visual field, but also by abnormal input representing the ipsilateral visual field. These novel findings help elucidate the nature of albino misrouting.

A lbinism has a profound effect on visual development and visual function.[1-3] In normal people, decussation of the optic fibres is loyal to the vertical meridian that passes through the fovea: fibres from the temporal retina project ipsilaterally to the lateral geniculate nucleus and cortex, whereas fibres from the nasal retina project contralaterally. In albinos, however, a higher than normal proportion of fibres from the temporal retina project contralaterally. The line of decussation is, as a consequence, shifted to the peripheral visual field. The impact of this abnormal visual projection on the cortical mapping of the visual field in human albinism has yet to be determined.

Clinically, the diagnosis of albinism is confirmed by measuring the visual evoked scalp potentials elicited by monocular full field pattern appearance (pattern onset-offset) stimulation. In albinos, the resulting visual evoked potential (VEP) is generally greatest at recording sites contralateral to the stimulated eye. It is this hemispherical VEP response asymmetry that is used as a diagnostic criterion in conjunction with the interocular reversal of this hemispherical asymmetry.[4 5] The reported sensitivity of using these criteria was remarkably high in one study (100% by Apkarian *et al*[6]), but other studies using similar criteria have reported lower sensitivities (45% by Bouzas *et al*[7]; 83% by Soong *et al*[8]; 18% by Jarry *et al*[9]). Furthermore, due to the limited spatial resolution, VEP investigations cannot contribute to specific questions of albino cortical organisation such as the representation of the visual field in the early visual areas and the degree of cortical magnification. Functional MRI (fMRI), however, has been used to elucidate visual cortical organisation in normal[10 11] and abnormal subjects[12-14] and has also been successfully employed to highlight lateralisation asymmetries on full field stimulation in human albinos.[15] Here we take the analysis of the albino visual cortical representation a stage further. We presented stimuli to each visual hemifield during VEP and fMRI measurements. Our aims were to compare VEP with

fMRI measurements that enable us to localise directly the sites of cortical activity.

METHODS
Subjects
A tyrosinase positive female albino, aged 62, was the subject for the experiments. The subject was tested with corrected visual acuity (6/18 right; 6/24 left eye). The right eye was the habitually fixating eye and the one that was tested in the hemifield stimulation experiments, while the other eye was patched. There was mild nystagmus of <2° in this eye during monocular viewing. When viewing through the left eye, nystagmus was greater and therefore was not suitable for testing with the stimuli we could present within the MR scanner. Control data are presented from a 32 year old normal man with no neurological or ophthalmological history. His left eye was tested in the hemifield stimulation experiments described here. Subjects gave their informed written consent. The study had approval from the Riverside ethics committee and the Royal Holloway ethics committee.

Visual stimulation: fMRI measurements
A contrast reversing (6 Hz) chequerboard stimulus (mean luminance 35 cd/m^2, contrast 90%) was presented monocularly on an LCD screen (NEC LCD2010). The chequerboard comprised a quarter annulus centred on fixation, symmetric above and below the horizontal meridian, and extending 2°–4.5° in eccentricity along that meridian (fig 1 B). The radial extent of each check increased linearly from 0.4° to 0.7° with eccentricity. Stimulation of the nasal and temporal retina was performed in separate experiments. The subjects were asked to fixate a black cross, which was visible throughout the experiment. The centre of the cross changed randomly between white and black at an average rate of 1.5 Hz to enhance its salience. The visual stimulation conformed to a "box car" design with a cycle defined as 18 seconds of chequerboard reversal followed by 18 seconds of a spatially uniform grey background. The stimulus cycle was repeated seven times in each experiment amounting to a total duration of 252 seconds.

fMRI acquisition
T2* MR images were acquired during visual stimulation using a Siemens Magnetom Vision 1.5T MRI system fitted with EPI gradient overdrive. A multislice two dimensional gradient echo EPI sequence (TE 54 ms, 128×128 matrix, 240 mm field of view, interleaved slice order with no gap) was used to measure the blood oxygenation level dependent (BOLD) signal as a function of time. Every 3 seconds eight 4 mm thick

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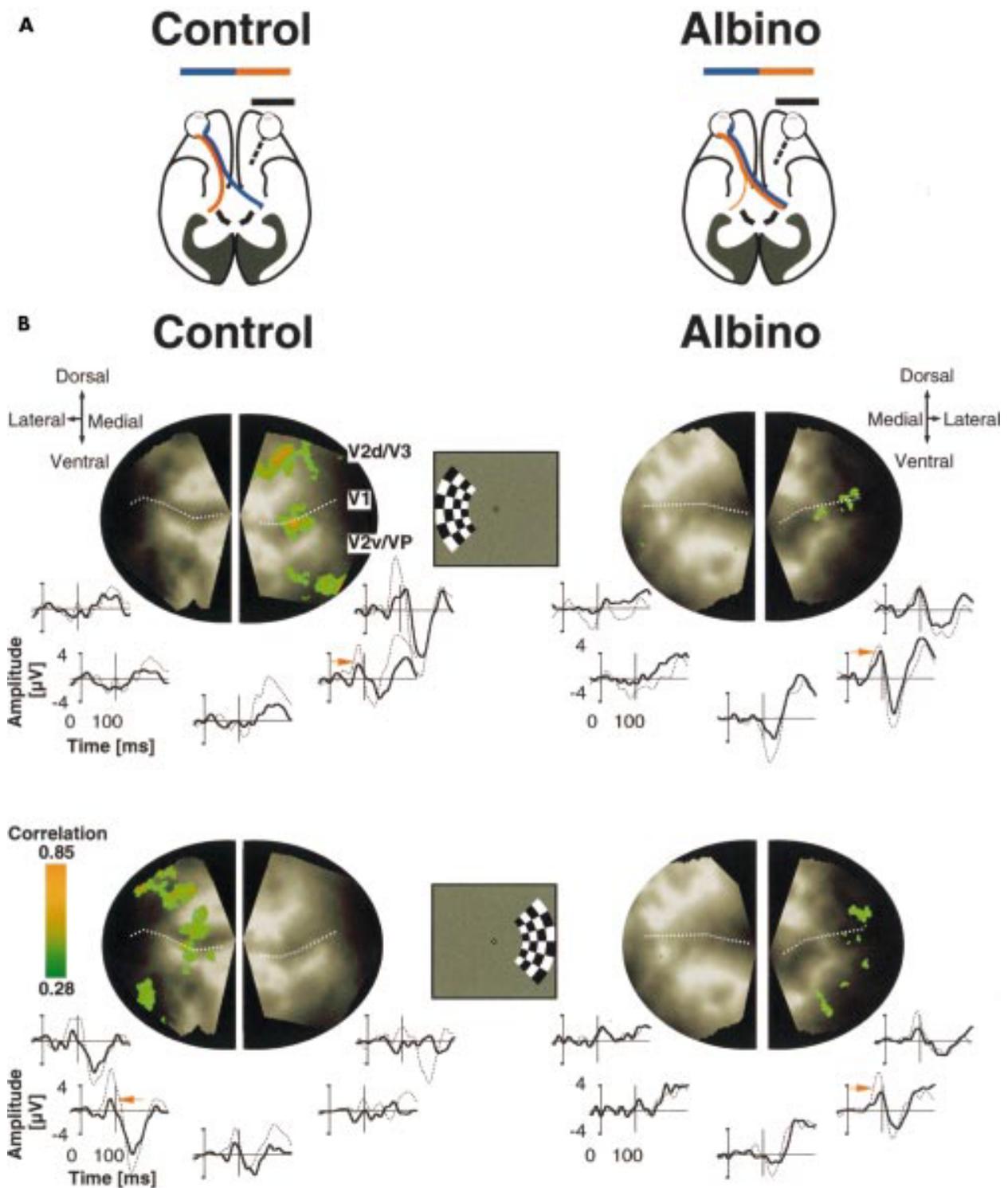
Figure 1 (A) Schematic depiction of the crossing of the optic nerves in normal subjects and albinos. In normal subjects the crossing is partial, whereas it is more complete in albinos. (B) Comparison of cortical activity after visual stimulation in a normal subject and an albino as determined with fMRI and VEP measurements. Control data are given on the left, albino data on the right. The top panels depict activity after stimulation contralateral to the stimulated eye, the bottom panels after stimulation ipsilateral to the stimulated eye. The VEP recordings are arranged according to the electrode distribution on the scalp (see methods); horizontal lines indicate baseline, vertical lines indicate 0 and 100 ms after stimulus onset, respectively. Traces in bold show responses to the stimulus with spatial dimensions identical to the fMRI stimulus. Dotted traces show responses to a slightly bigger stimulus, comprising the left/right central 4.5°, used to enhance the VEP response. fMRI data are superimposed on the flattened representations of the occipital lobe, where the dotted lines indicate the fundus of the calcarine sulcus. The left and right parts of each panel show the occipital lobe ipsilateral and contralateral to the stimulated eye, respectively. Unilateral monocular hemifield stimulation elicits corresponding responses in VEP and fMRI: fMRI activity in the normal subject is contralateral to the stimulated visual field, but in the albino it is contralateral to the stimulated eye independent of the stimulated field. This is consistent with the lateralisation of the C1-VEP component indicated by the arrows for each subject and condition.

slices were acquired perpendicular to the calcarine sulcus in a 128×128 grid covering a field of view of 240×240 (voxel size 1.82×1.82×4 mm) for a duration of 252 seconds, yielding 84 temporal samples. The volume of cortex sampled has been shown to be sufficient to document activity in the normal early visual areas[14] for the field sizes used in the experiments presented here.

Cortical flattening and fMRI analysis

T1 weighted MR images (voxel size: 0.98×0.98×1 mm) were used to create a flattened representation of the cortical grey matter.[17][18] After registration of the T2* weighted images to the T1 weighted image's coordinate frame, the fMRI time series were projected onto the flattened representation.[11] Each voxel's time series underwent the following anaysis: (1) The first cycle of stimulation (12 temporal samples) was discarded from analysis to avoid transient onset artefacts associated with magnetisation not reaching a steady state, (2) the linear trend over the 84 temporal samples was removed, (3) the time series was divided by the mean intensity of the voxels, (4) Fourier analysis was applied to obtain the amplitude and phase for each frequency, and (5) the correlation with respect to the fundamental frequency of the visual stimulation, 1/36 Hz, was calculated. The correlation coefficients in the flattened representation were blurred by convolving a gaussian kernel (size 5×5 mm, half width 1 mm) with the complex vector representation of the BOLD response. The value at which a voxel's correlation coefficient deviated from those of a noise distribution on a 5% basis was taken as threshold to determine which voxels were driven by the input stimulus. The blurred correlation coefficients, which exceeded the correlation threshold and with phase values of –2 to 9 seconds with respect to stimulus onset were then plotted on the flattened representation in false colour.

VEP recordings

Five channel VEPs were recorded using standard techniques. Surface electrodes were situated posteriorly in the midline 2.5 cm above the inion, and at lateral spacings of 4 and 8 cm from the midline. These were referred to a linked ears reference. Signals were amplified, filtered (1–100 Hz) and digitised at a sampling rate of 1000 Hz. At least 180 trials/condition were collected. Offline, averaged sweeps were digitally filtered (0–40 Hz). Baseline was defined as the mean value from 0 to 50 ms of the averaged trace and used as zero reference for peak measurements. The stimulus was a circular black and white circular chequerboard centred around fixation (mean luminance 30 cd/m², contrast 98 %). For the full field experiments we stimulated within a circular aperture of 4.5° radius. For the hemifield experiments we stimulated exactly the same crescent shaped region of the visual field as we did in the fMRI experiments (see above). Because this yields only low VEP amplitudes we repeated the experiments with a stimulus comprising the full left or right central 4.5°. For each of these conditions the stimulus presentation was pattern onset of 33 ms and pattern offset of 483 ms. We applied pattern onset as opposed to pattern reversal stimulation used in the fMRI experiments, as it (*a*) yields reliable responses in subjects with nystagmus and (*b*) allows more reliable localisation of the cortical generator of VEP signals as it is not confounded by paradoxical lateralisation.[16]

RESULTS

The VEPs in the normal subject showed no pronounced interhemispheric asymmetry with full field stimulation (C1 amplitudes at recording site 4 cm left v 4 cm from right Oz: left eye stimulated: 4.0 v 5.4 μV; Right eye stimulated: 2.9 v 4.1 μV). By contrast, the responses from the albino showed a strong hemispheric asymmetry, with the responses from each eye being greatest at the contralateral electrodes (C1 amplitudes

at recording site 4 cm left v 4 cm right from Oz: Left eye stimulated: 1.0 v 5.9 μV; right eye stimulated: 5.9 v 0.7 μV), clearly showing the VEP lateralisation which is characteristic for albino misrouting.

In the normal subject separate stimulation of the hemifields resulted in VEP responses that were clearly lateralised to the hemisphere contralateral to the stimulated hemifield. By contrast, and independent of the stimulated hemifield, the VEP responses in the albino were larger at recording sites contralateral to the stimulated eye (fig 1 B). The fMRI data confirmed that both hemifields in the albino were represented in the cortex contralateral to the eye being stimulated, rather than contralateral to the hemifield being stimulated (fig 1 B). Activity in the normal cortex is located in the fundus of the calcarine (primary visual cortex). Dorsal and ventral to this region there are areas of activation consistent with representations of the V2/V3 boundaries as determined with retinotopic mapping procedures. The occipital cortex is also active in the albino, but on the hemisphere that is contralateral to the stimulated eye regardless of which hemifield is stimulated. The activity could not be assigned to a particular visual area because retinotopic mapping procedures failed to identify visual area boundaries in this subject. The activity in the albino cortex was, however, located in and around the calcarine sulcus as indicated in figure 1 B. The fMRI signal in the albino was strongly reduced in comparison with that found in the normal subject, which is likely to be attributed to impairment of visual functions such as low visual acuity and fixation instability. Although only the habitually fixating eye was tested in experiments where hemifield stimulation was employed, other experiments in which we stimulated both hemifields of this albino disclosed activity contralateral to each of the two eyes as reported previously.[15]

DISCUSSION

This study presents novel data comparing the electrophysiological and fMRI responses to hemifield pattern stimulation in albino misrouting. The full field VEP recordings in the albino are characteristic of albino misrouting,[4–6] such that the potentials evoked by stimulation of either eye are maximal in traces from the contralateral hemisphere. The data from hemifield stimulation indicate that this is due to a representation of both right and left visual fields in the cortex contralateral to the stimulated eye, consistent with previous results.[19] The fMRI data directly show that in the albino it is indeed the occipital lobe contralateral to the stimulated eye that is active during stimulation in each hemifield, whereas in the control subject hemispheres are only active during stimulation in the contralateral visual field. Activity ipsilateral to the stimulated eye is strongly reduced in the albino. By contrast, Hedera *et al*[15] report in their fMRI study of human albinos substantial residual ipsilateral activity in the more anterior portion of the fundus of the calcarine sulcus. The difference between their study and ours is the size of the visual stimulus. The full field stimulus used by Hedera *et al*[15] results in stimulation of the outer temporal retina, fibres from which remain ipsilateral in albinos. It is not surprising, therefore, that Hedera *et al*[15] document some cortical activity ipsilateral to the stimulated eye, whereas we do not. It should be noted that in the control subject the topographic distribution of the fMRI signal already allows the estimation of the location of the early visual areas. Such an interpretation of the topographic distribution of the cortical activation pattern in the albino is, though tempting, impeded by the low signal strength, which, after thresholding of the data, yields only incomplete information about the topographic layout of the response.[20] Finally, whereas the fMRI responses of the albino are smaller than those of the normal subject, the pattern onset VEP responses are greater. This contradistinction is likely to be associated with the large intersubject variability in VEP

amplitudes, which is partly due to variables independent of neuronal activity—for example, the individual brain and skull morphology.

It is now of great interest how the topographic cortical representation of the visual field is established as there are conflicting reports on the pattern of the cortical representation in other species.[1]

ACKNOWLEDGEMENTS

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NEUROLOGICAL STAMP...

Nikola Tesla (1856-1943)

The advent of magnetic resonance scanners has drawn the term "Tesla" into the neurological vocabulary, by denoting as it does the strength of the magnet used . Tesla was born in Luka, Croatia, on the Adriatic coast and studied mathematics and physics at the University of Graz and philosophy at Prague. In 1884 he immigrated to the United States where he worked for Thomas Edison, until a bitter quarrel developed between them. Tesla invented the first alternating (AC) motor in 1887. Most commercially generated electricity at the time was direct current (DC). Edison was a dedicated adherent of the dc system but Telsa saw fundamental weaknesses in this system. He recognised that the main advantage of the AC system was that, with transformers, it was easier and cheaper to transmit very high voltages over very long distances. He soon popularised the AC system, making it practical with out of step currents and rotating magnetic fields. Tesla's invention was taken over by Westinghouse and led to intense competition with Edison and other DC users. The ac system replaced DC electricity which, became confined to specialised uses.

Tesla also became involved in *x* ray research. One theory of the time was that blindness might be cured by *x* rays. Tesla pointed out that there was no evidence for this. He was however convinced he had with *x* rays discovered a way of stimulating the brain and he repeatedly exposed his head to radiation. With exposures of 20 to 40 minutes he was able to show the bony outline of the skull, the orbit, mandible, and the connection of the vertebral column to the skull. He was the first to suggest that *x* rays could be used therapeutically—perhaps to "project chemicals into the human body".

Telsa had a most fertile mind. His work in science was vast and only a few contributions have been mentioned. His inventions brought him
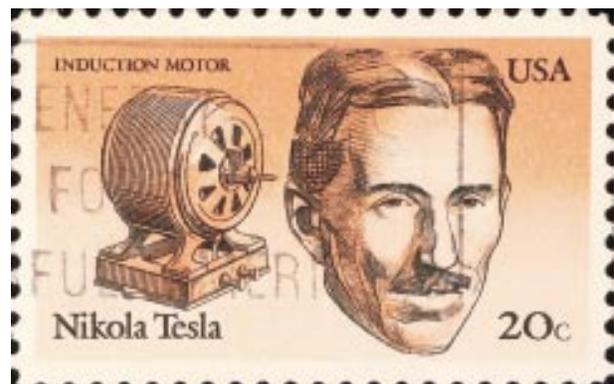
little acclaim during his lifetime. There had been speculation on quite reasonable grounds that he refused the Nobel Prize, and he may have been the only scientist to do so. He died a relatively poor man. The United States philatelically honoured him in 1983 along with three other American inventors (Stanley Gibbons 2050, Scott 2057). His name is often misspelled and Tesla once wrote to a friend that he wished he could turn all the forked lightning in his laboratory on critics who misspelled his name.

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