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Recovery of vision and pupil responses in optic neuritis and multiple sclerosis

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Abstract

The recovery of visual performance and pupil responses were investigated in patients with demyelinating optic neuritis (ON) and multiple sclerosis (MS). The pupil constriction amplitude and the time delay (latency) of the pupil response were measured in 14 patients with a history of unilateral ON in response to either achromatic (luminance) or chromatic (isoluminant) stimulus modulation. Five of these subjects were diagnosed later with MS. In addition, we measured detection thresholds for achromatic stimuli using standard visual field perimetry and chromatic thresholds using a new colour assessment and diagnosis (CAD) test that isolates the use of colour signals. The results show that, despite significant improvements in visual function following the acute phase (as assessed using visual acuity and fields), significant pupil response deficits remain. The findings also demonstrate that accurate measurements of pupil responses and chromatic thresholds can reveal deficits that remain undetected with more conventional techniques. These preliminary findings suggest that the techniques described here can provide useful information about remitting and relapsing demyelinative phases, often observed during MS and ON.

Keywords: colour, demyelination, multiple sclerosis, optic neuritis, pupil

Introduction

Optic neuritis (ON) is an inflammation of the optic nerve that affects mainly the young adult population (Beck, 1991; Hickman *et al*., 2002; Kidd *et al*., 2003; Beck *et al*., 2004; Balcer, 2006). The term 'optic neuritis' usually refers to a demyelinating optic neuropathy, such as occurs in multiple sclerosis (MS). It typically results in subacute loss of vision accompanied by mild ocular pain. The severity of visual loss ranges from a slight visual deficit to complete loss of light perception.

Most patients recover visual acuity almost completely but in the long term there can be residual loss in vision and quite frequently, as shown here, a pupil sensitivity loss even when visual function is almost normal. The proportion of ON cases developing MS can be as high as 50% (Optic Neuritis Study Group, 1997) and the risk of developing MS after ON increases over time (Druschky *et al*., 1999; Dalton *et al*., 2002; Beck *et al*., 2004). Optical coherence tomography (OCT) of the retinal nerve fibre layer (Trip *et al*., 2005; Costello *et al*., 2006) and magnetic resonance imaging (MRI) can demonstrate lesions in the optic nerve (Hickman *et al*., 2004; Audoin *et al*., 2006) but there remains a need for non-invasive, inexpensive and rapid techniques to monitor disease progression and rule out further neurological complications.

The most common clinical assessment of pupil function during optic nerve lesions is based on examining for a relative afferent pupil defect (RAPD). Although rarely performed in the clinic, the RAPD can be quantified by placing a series of neutral density filters of increasing strength in front of the asymptomatic eye of the patient until the pupil constriction elicited by an alternating light is the same in both eyes. The RAPD is then measured in

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log units as the light attenuation needed to match the constriction amplitude in the two eyes. A RAPD of 0.3 log units or more is usually considered as a reliable sign of pupil dysfunction (Kardon, 1995). In this study we measured directly asymmetries in pupil constriction amplitudes in response to sinusoidal modulation of a stimulus presented separately to the affected and to the unaffected eye. The accuracy of these measurements is high with a measurement precision of 0.01 mm (Alexandridis *et al*., 1992). The new technique is effectively a dynamic version of the simple RAPD test with a number of significant advantages (Barbur, 2004b).

Previous studies of the pupil response in ON and MS using clinical techniques have already revealed the existence of residual RAPD that persisted well after recovery of visual acuity (Ellis, 1979; Fison *et al*., 1979; Alexandridis *et al*., 1981; Fleishman *et al*., 1987; Cox, 1989). There are reports of a reduced pupil light reflex even in MS patients with no previous history of ON or other eye problems (Pozzessere *et al*., 1997). Previous studies have measured only changes in the pupil response to luminance change, but here we report the pupil colour response also. Isoluminant stimuli are widely used in many areas of vision research as there is strong evidence from electrophysiological recordings in animals that achromatic and chromatic signals are carried by substantially different neurones. This functional segregation occurs very early in the visual pathways, at the level of the optic nerve before reaching the lateral geniculate nucleus (Kaplan and Shapley, 1986; Shapley, 1990). There is therefore much interest in applying this recent knowledge of the anatomy and physiology of the visual pathways to the development of new tests for non-invasive assessment of visual anomalies.

Subjects and methods

We measured pupil responses, chromatic thresholds, visual acuity and visual fields in a group of 14 patients (4 male, 10 female) with a history of ON, five of whom were also diagnosed with multiple sclerosis (MS). Patients' age range was 26 to 53 years. At the time of examination, within 3 to 60 weeks after the initial attack (mean 29 weeks), a large number of patients showed visual acuity that had recovered spontaneously to normal or near-normal levels, although they often were reticent to accept that their vision was completely normal. A group of 15 subjects provided control data for the pupil test. A separate group of 120 subjects provided 95% confidence intervals for chromatic thresholds in the normal population. All subjects in these two control groups had normal or corrected-to-normal vision and were within the age range of the patient group. Written consent was obtained from each subject and the study was approved by the Research and Ethics Committees of City University and of Moorfields Eye Hospital. The tenets of the declaration of Helsinki were followed.

Visual acuity and Humphrey visual fields

Visual acuity was measured in each subject using a logMAR (log of the minimum angle of resolution) letter chart (Bailey and Lovie, 1976) at a viewing distance of 6 m. Each row of the logMAR chart is scaled in a geometric progression of 0.1 log units and it is thus more convenient than other charts (e.g. the Snellen chart) to investigate correlations of visual acuity with visual field perimetry or pupil sensitivity loss. As Snellen notation is widely used clinically, a conversion from logMAR to Snellen values is used in the figures. Normal visual acuity (Bailey and Lovie, 1976) is usually defined as logMAR value of 0.0 (corresponding to a resolution angle of 1 min of arc and to a Snellen value of 6/6 in metres or 20/20 in feet).

Visual fields were tested using the Humphrey Visual Field Analyzer program 30-2 (Zeiss Humphrey Systems, Dublin, CA, USA), which measures luminance detection thresholds across 30° of the visual field. Observers carried out a practice session before the actual test. The severity of visual field defects was quantified as the mean deviation (in dB), which is the centre-weighted difference in the visual threshold compared with a population of age-matched normal subjects. A mean deviation larger than 3 dB is often considered abnormal (Haley, 1987).

Pupil measurements

The PSCAN system, designed and built at the Applied Vision Research Center in London, UK (Barbur *et al*., 1987), was used to record the pupil diameter by fitting the best circle to the pupil at a rate of 50 Hz. Patients viewed a calibrated computer display at a distance of 70 cm. Each eye was tested under monocular viewing, with an infrared transmitting filter (IR860, Kodak, Rochester, NY, USA) covering the other eye to block the light from the computer display, but allowing the simultaneous pupil size recording of both the stimulated (direct response) and the non-stimulated eye (consensual response). Total testing time was approximately 15 min. Pupil responses were also measured in a control group of 15 age-matched healthy subjects with normal vision under identical experimental conditions employed during the testing of the patient group. Pupil responses were measured for each eye in the control group to exclude the possibility of any abnormal difference between the two eyes. The left and right eye response amplitudes were virtually identical for each

Table 1. Summary of mean pupil constriction amplitudes and latencies in a group of 14 patients with previous history of unilateral optic neuritis

	Amplitude (mm)			Latency (ms)		
	Affected	**Unaffected**	**Normal group**	**Affected**	**Unaffected**	**Normal group**
Pupil luminance response						
Affected eye	0.21 ± 0.02			537 ± 21		
Unaffected eye	$p < 0.01$	0.31 ± 0.03		n.s.	521 ± 18	
Normal group	$p < 0.01$	$p = 0.04$	0.37 ± 0.03	$p < 0.01$	$p < 0.01$	468 ± 12
Pupil colour response						
Affected eye	0.13 ± 0.02			631 ± 20		
Unaffected eye	$p < 0.05$	0.18 ± 0.02		n.s.	588 ± 20	
Normal group	$p < 0.01$	n.s.	0.21 ± 0.03	$p < 0.01$	$p < 0.05$	550 ± 12

The mean response amplitudes and the corresponding standard errors are tabulated in each column for both the affected and the unaffected eyes in the optic neuritis group. The probability (p-values obtained from pairs of t-tests as described in the text) that there is no difference between each mean is given at the corresponding row–column intersection.

subject in the control group. We randomly selected either the left or the right eye response of each control subject to compute the mean response and an estimate of inter-subject variability in the normal population (i.e. the 95% confidence intervals as shown in *Figure 2* and standard errors in *Table 1*). In the patient group we tested for a reduced pupil response of the affected eye compared with the unaffected or asymptomatic eye. In spite of most of the patients showing symptoms in only one eye, it is also interesting to compare the asymptomatic eye against the control group because the other eye is also often affected to some extent, which might be indicative of disease progression. Pupil responses in the patient group were considered abnormal when constriction amplitude in any eye was considerably smaller that the lowest 95% limit, or the interocular difference exceeded 0.04 mm which is well above the maximum interocular difference of 0.02 mm observed in the control group.

PLR and PCR

Besides the pupil response to luminance changes, the pupil is also known to respond to colour changes, even in the absence of a total light flux change (Barbur *et al.*, 1992). In order to isolate the pupil colour responses (PCR) from the classical pupil light reflex (PLR) response, the coloured target was chosen to be doubly isoluminant with respect to the achromatic background i.e., in addition to being photopically isoluminant the stimulus also generated zero rod contrast (Young and Teller, 1991).

The visual stimuli were generated on a calibrated computer display at a viewing distance of 70 cm. Two stimuli were used, either an achromatic disc modulated in luminance, or a red-coloured disc modulated in chromatic saturation but remaining isoluminant with the background. Both discs subtended a visual angle of 7° and were presented foveally on a uniform achromatic background ($30° \times 24°$) of 16 cd m^{-2} with CIE chromaticity co-ordinates $(x,y) = (0.305, 0.323)$. Both luminance and chromatic saturation were modulated sinusoidally at a frequency of 1 Hz for a period of 10 s. This frequency was chosen from preliminary studies so as to achieve a large pupil constriction without compromising the signal-to-noise ratio of the response. The mean luminance of the achromatic disc was 32 cd m^{-2} reaching a maximum value of 64 cd m^{-2}. The maximum chromatic saturation possible with the phosphors of the display under the double isoluminant constraint was 0.16 units of distance in the xy CIE colour space. A minimum of 16 traces were averaged for each eye and both the pupil amplitude and the time delay of the response were computed from the fundamental harmonic of the discrete Fourier transform (DFT) of the averaged trace (*Figure 1*). Typical parameters of interest in a pupillogram are the amplitude of the constriction (in mm) and the time delay in the response (in ms). Other parameters make it possible to check for the reliability of the response: the signal-to-noise ratio, and the nonlinearity index which indicates the contribution from harmonics other than the fundamental in the DFT analysis of the response. *Figure 1* shows details of stimulus modulation and the pupil response traces of a typical patient.

CAD test

Colour vision was tested in 10 of the 14 patients for both the affected and the unaffected eyes using the colour assessment and diagnosis (CAD) test. Chromatic thresholds, defined as the minimum colour saturation needed to distinguish a coloured target embedded in an achromatic background, were measured for 18 different directions (colours) in the CIE xy-1931 colour space (Wyszecki and Stiles, 1982). The CAD test and principles involved in using dynamic background-masking techniques to isolate the processing of certain stimulus attributes such as chromatic signals have been described

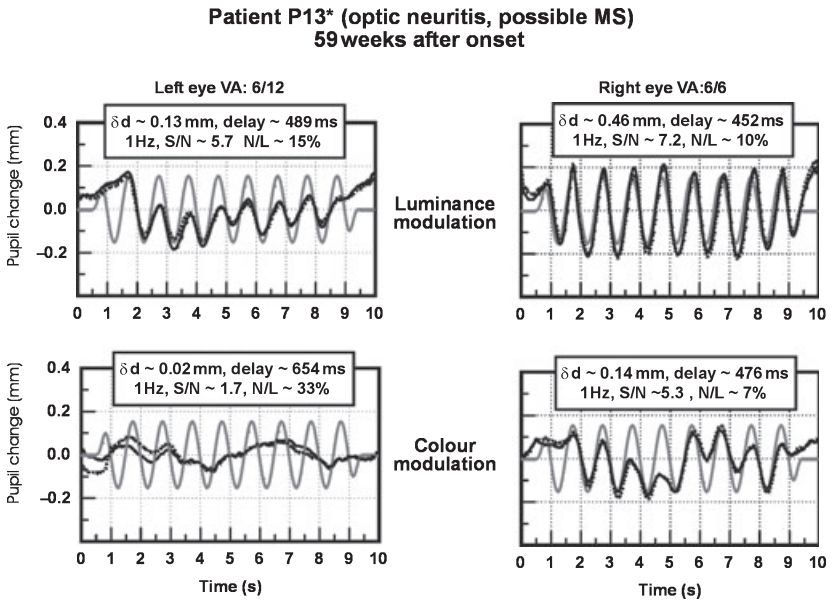

Figure 1. Example of averaged pupil response traces elicited by either luminance (top) or isoluminant colour modulation (bottom) of a central stimulus disc presented separately to the affected eye (left) and the asymptomatic eye (right) in a patient who had been diagnosed with unilateral optic neuritis 59 weeks earlier and was presenting symptoms of multiple sclerosis. The pupil constriction amplitude (δd), response latency (time delay in ms), signal-to-noise ratio (S/N) and a measure of pupil response non-linearity (N/L) were computed by evaluating the Discrete Fourier transform of the averaged trace.

in detail elsewhere (Barbur *et al*., 1994; Barbur, 2004a) and an online demonstration is also available at www.city.ac.uk/avrc/colourtest.html.

During the CAD test the subjects viewed the same visual display used for pupil measurements from a distance of 70 cm. The display subtended a visual angle of $24° \times 30°$. During each stimulus presentation, the colour-defined stimulus is shown moving diagonally across a square made up of random luminance contrast noise, in one of four possible directions. The duration of the stimulus was 600 ms and the centre square region subtended a visual angle of 6°. The luminance of the achromatic background field was 12 cd m^{-2} and the colour-defined stimulus was isoluminant with respect to the background. The stimulus was buried in dynamic luminance contrast noise to mask the detection of possible luminance contrast signals that can arise as a result of inter-subject differences in spectral luminous efficiency function. The noise mask covered the square region and was composed of smaller checks (0.24°) each of which varied randomly in luminance within ±16% of background luminance. The refresh rate of the monitor was 75 Hz and the spatial noise changed every 53.3 ms. The subject's task was a four-alternative forced-choice discrimination of the direction of stimulus movement. Threshold was determined by a two-down, one-up staircase (Levine, 2000), which starts reducing colour intensity with an initial step size of 0.006 CD units until observers cannot distinguish the coloured moving targets from the achromatic background. Observers continue this staircase procedure during nine reversals. Each reversal reduces the step size by 0.001 CD units until a step size of 0.002 CD units is reached. Chromatic thresholds are then computed by averaging the chromatic distance in the CIE *xy*-1931 (Wyszecki and Stiles, 1982) colour space presented in the last four reversals of the staircase. The parameters of the staircase and the test have been optimized during previous pilot studies in the normal population. All subjects and patients carried out an initial practice session prior to the test using a fast converging staircase (four reversals, initial and final step size of 0.01 and 0.006 respectively). End CD values of the practice sessions were used as starting values in the actual test. We were thus confidence that colour thresholds were computed with sufficient accuracy (0.002 CD units) and reliability for each subject.

Chromatic thresholds for each patient and normal trichromats (see *Figure 4*) were fitted using an ellipse-specific algorithm (Fitzgibbon *et al*., 1999). The axes of the fitted ellipse determine the chromatic thresholds along the yellow–blue (YB) (major axis) and red–green (RB) (minor axis) directions in the CIE colour space. The lengths of the minor and major axes of the mean ellipse obtained from a group of 120 normal trichromats provide the 2.5% and 97.5% limits of the distribution of chromatic thresholds for the ''standard'' CAD observer.

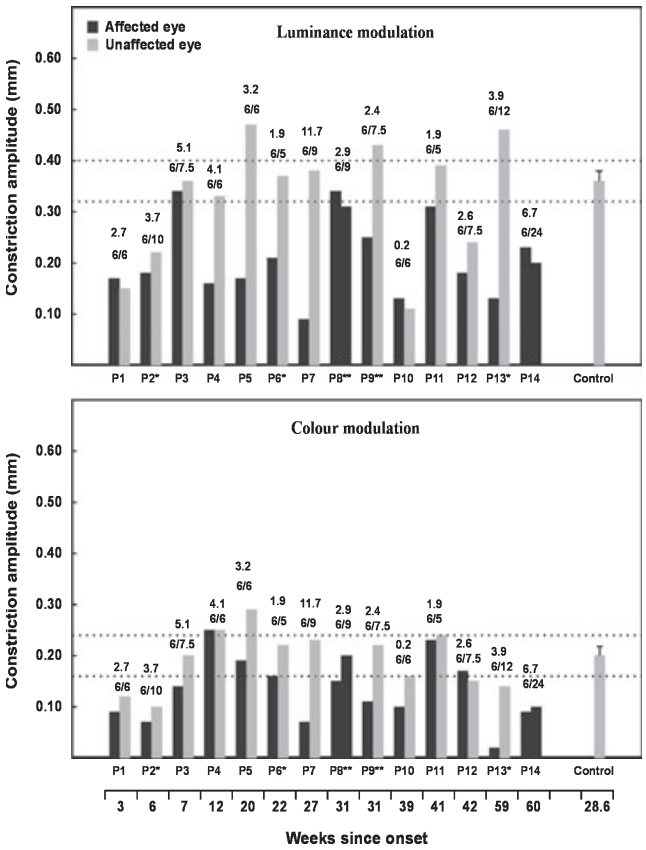

Figure 2. Bars show pupil constriction amplitudes in response to luminance (upper section) and chromatic contrast (lower section) measured in a group of patients several weeks after the onset of demyelinating optic neuritis. The dotted lines indicate the 95% confidence interval around the mean response obtained for the same stimulus conditions in an age-matched control group (15 subjects). Above each set of bars, decimal numbers indicate a measure of visual field sensitivity loss (mean deviation of the affected eye in dB obtained with the Humphrey visual field analyser). The fractions indicate the corresponding Snellen acuity. The diagnosis was bilateral in two patients (P8 and P14, both eyes shown with dark bars). Another five patients were diagnosed with possible (P2, P6 and P13, indicated with *) or definite (P8 and P9, indicated with **) multiple sclerosis.

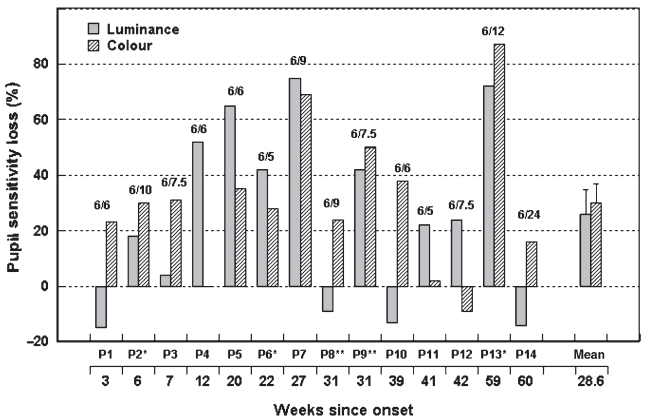

Figure 3. The bar charts plot a measure of pupil sensitivity loss for both colour and luminance contrast modulation. The number of weeks since the initial episode of optic neuritis and the corresponding Snellen acuity of the affected eye are shown separately for each subject investigated. The percentage of pupil sensitivity loss was computed as the ratio of the interocular difference in constriction (when each eye was stimulated separately) to the response amplitude measured in the eye diagnosed initially as 'unaffected'.

Results

Pupil responses to luminance and colour

The averaged mean and standard error of the pupil response following stimulation of the affected eyes are summarised in *Table 1* together with similar data measured in the asymptomatic eyes of ON patients and in the control group of 15 subjects. To test the significance of the differences in mean values, a paired *t*-test was used when comparing the affected versus the unaffected eyes and an independent *t*-test when considering differences with the normal group. The probability indicating the absence of a significant difference between the mean values obtained for each of these tests is indicated at each row–column intersection in *Table 1*. The application of a Bonferroni correction for the three comparisons considered for each data set changes the level of significance from 0.05 to 0.015 (Howell, 2002). This correction reduces the possibility of finding significance by chance during multiple comparisons, but increases the possibility of erroneously considering a *p*-value higher than 0.015 as not significant (e.g. patients' responses will be classified as normal when they are in fact abnormal). In any case, the results that are discussed below are independent of this correction.

Affected eyes

Despite the large inter-subject variability in pupil amplitude (*Figure 2*) and the small number of patients tested, averaged mean effects in *Table 1* reveal abnormal pupil responses in the affected eyes compared with the normal control group, with significantly reduced amplitudes and increased latencies ($p < 0.01$). The significant increase in the time delay of the response (about 75 ms for luminance modulation and 80 ms for colour) compared with the normal group, together with the decrease in the amplitude of the constriction, confirms that pupil function is often reduced in ON.

However, given the large variability in recovery rates and time elapsed since initial onset, overall computation of significance in group means is not always fully informative, particularly in such a heterogeneous patient group. In practice, it is better to test each patient's response against an age-match control group or monitor changes in responses across time whenever possible. For

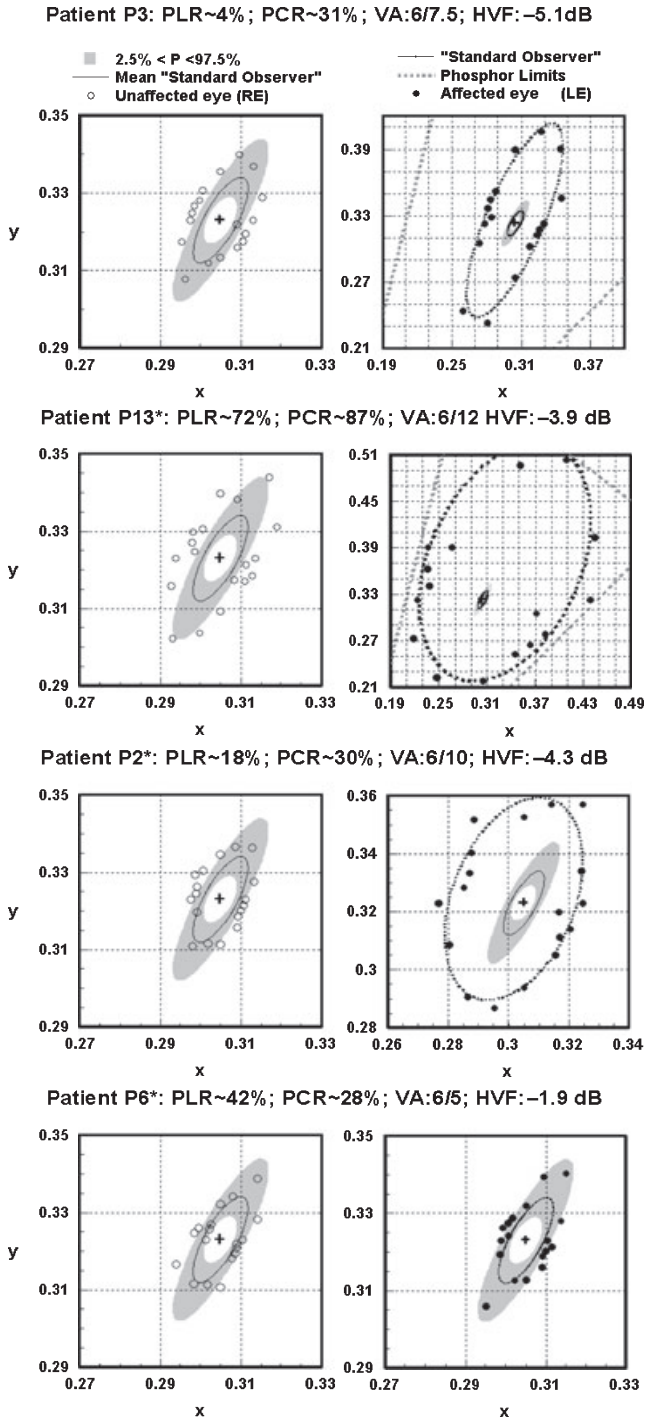

Figure 4. Examples of chromatic discrimination thresholds in four patients. Thresholds measured in the affected eye are shown on the right with the corresponding results in the asymptomatic eye shown on the left. Other indicators of pupil and visual function are shown individually above each panel graph for the affected eye only: pupil luminance response (PLR) and pupil colour response (PCR) deficits; Snellen visual acuity (VA) and Humphrey Visual Field (HVF) scores. The grey area bounded by the two ellipses is defined by the 2.5% and 97.5% limits of the distribution of thresholds in 120 normal trichromats. The solid black ellipses correspond to the averaged threshold for the ''standard'' CAD test observer.

instance, only patient P3 (upper panel of *Figure 2*) showed pupil light responses (PLR) without any clear sign of a pupillary deficit (i.e. no clear inter-ocular difference and both responses within a 95% confidence interval of the control group). On the other hand, this same patient showed an abnormal pupil colour response (PCR), visual field (mean deviation >3 dB), and acuity (worse than 6/6), which illustrates the convenience of using multiple tests when assessing optic nerve damage.

As for the pupil colour response (lower panel of *Figure 2*), only two patients (P4 & P11) showed responses that were clearly within the normal range and without significant inter-ocular difference (*Figure 2*, lower panel). In contrast, both patients showed a clear inter-ocular difference in the luminance response although both had recovered visual acuity. This result in particular seems to reflect a general trend: patients who fully recovered visual acuity to normal levels (6/6 or better) still revealed a persisting deficit in the PLR.

Asymptomatic eyes

Interestingly, data for the asymptomatic fellow eyes revealed slightly longer mean latencies and reduced mean amplitudes in comparison with the normal group. These effects were generally not significant due to the large inter-subject variability. These findings do however suggest that the asymptomatic fellow eye was probably also affected to some extent in several cases. This is also confirmed by the reduced pupil response amplitudes for the 'unaffected' eye shown in a number of patients (*Figure 2*). Asymptomatic demyelination of the optic nerves in MS has also been reported in evoked potential studies (Hess and Plant, 1986; Brusa *et al.*, 1999, 2001).

Pupil sensitivity loss, visual acuity and visual fields

The full recovery of the visual and pupillary function several weeks after the onset of the disease is rarely complete. In fact, we can see from *Figures 2 and 3* that all patients reveal some type of deviation from either normal visual field, acuity or pupil function.

In addition, neither the recovery of the visual function nor the pupil sensitivity appeared to be related to the time elapsed since the onset of the disease, with some cases showing large deficits even after 4 months while others recovered substantially in a matter of 4–6 weeks. Despite nearly every patient showing some type of pupillary deficit compared with the control group, a large proportion of patients showed normal or near-normal visual acuity (six patients with a value of 6/6 or better) and visual field sensitivity (only five of the 14 cases showing a mean deviation larger than 3 dB). This is also illustrated in *Figure 3*, where the pupil response deficit is plotted together with the values of the Snellen

visual acuity for each subject. The pupil deficit is evaluated as the pupil response difference between the affected and the unaffected eyes relative to the response of the good eye. This form of analysis yields a measure of the inter-ocular difference, and is more appropriate when one wishes to compare pupil responses to luminance and colour modulation. Small or negative values in *Figure 3* do not always imply a recovery, but instead may correspond to patients with a worsening of the eye previously diagnosed as unaffected (comparison of responses with a previous measurement or with a control group can usually provide more information). Small negative values ($< 10\%$) may also occur when a patient recovers pupil function completely, as a result of inter-ocular variability. In this study, the variability in pupil response amplitude between the two eyes in the control group was less than 10% (0.02 mm). This finding implies that for the experimental conditions employed in this study, a pupil deficit above 10% would be indicative of abnormal pupil function. In practice, a confirmation of a small pupil deficit would require further comparison with a control group and also testing the patient several times and/or on different days to test whether the inter-ocular difference persists or is a result of natural variability between the two eyes.

The large differences in both visual acuity and pupil response during recovery make it difficult to establish a minimum time for complete recovery. This large variability can be due to different recovery rates depending on the severity of the initial attack, but also to recurrent phases of the disease. As shown in *Figures 2 and 3*, many patients with normal or near-to-normal visual sensitivity (a visual acuity of 6/6 or better and mean deviation < 3 dB) have significant pupil response deficits, even a long time after the episode of ON was thought to be resolved. Since recovery in visual and pupil function are not always correlated, our results indicate that accurate measurements of the pupil responses can provide additional useful information to complement standard evaluation of visual sensitivity.

Colour vision loss

Chromatic thresholds for four different patients are plotted in *Figure 4*. The results show large inter-subject variability and reveal independent relations between visual and pupillary deficits. For instance, patient P3 almost completely recovered visual acuity (6/7.5) after 7 weeks from the initial episode of ON and showed a normal pupil response to light (4% deficit), but she still exhibits a large increase in colour discrimination thresholds for all directions tested in the *xy* CIE colour space. On the other hand, patient P6 is an example of poor correlation between pupillary and visual functions (*Figure 4*, lower panel). This patient showed normal colour vision, normal visual fields and acuity (6/5), but still presented a significant pupil deficit to both luminance and colour (PLR = 42% PCR = 28%). Finally, patients P13 and P2 (both diagnosed with MS) showed much increased chromatic detection thresholds and a greater deficit in the PCR compared with the PLR.

Another interesting finding is that the asymptomatic 'unaffected' eye often yields colour thresholds that fall just outside the normal range (the grey area shows the 95% confidence interval from a sample of 120 normal trichromats). Small colour deficits often remain undetected with conventional colour tests (Barbur, 2004a) and, because the fellow eye is sometimes affected to a lesser extent during ON, there is a need for sensitive tests to monitor disease progression.

The mechanisms for red-green (RG) and yellow-blue (YB) colour discrimination have different retinal circuitry and the neural signals are carried by morphologically different retinal ganglion cells (Dacey, 1996; Calkins, 1999). This has led to speculation on possible hue-selective deficiencies in lesions of the optic nerve. A frequently stated view is that, in ON, RG defects are predominant over YB (Flanagan and Zele, 2004). However, the data do not seem to support this hypothesis. All the patients revealed increased colour detection thresholds for each colour direction investigated (as defined in the CIE *xy* diagram) as illustrated in *Figure 4* (right column) for four patients. There was no spared direction and the loss of chromatic sensitivity affected both the RG and the YB axes. Furthermore, direct comparisons of the loss of colour sensitivity along the RG axis with the YB axis in the patient group (*Figure 5a*) did not show any evidence of predominant loss along any of these colour axes. In general, the results show larger inter-subject variability in threshold values along the YB axis in comparison with the variability observed in RG thresholds in the normal trichromat population (*Figure 5c*) and in the asymptomatic eyes of the patient group (*Figure 5b*). Similar results supporting the lack of colour-specific defects in ON have been reported in other studies (Mullen and Plant, 1986; Russell *et al.*, 1991; Schneck and Haegerstrom-Portnoy, 1997; Sartucci *et al.*, 2001).

Discussion

Recovery of visual and pupil deficits

The comparison between loss of pupil and visual response sensitivities reported here has shown that significant improvement in visual performance (as measured using colour discrimination, visual acuity and fields) is not always accompanied by an equal recovery of the pupil response (*Figures 2 and 3*, see also patient P6 in *Figure 4*). This observation suggests that

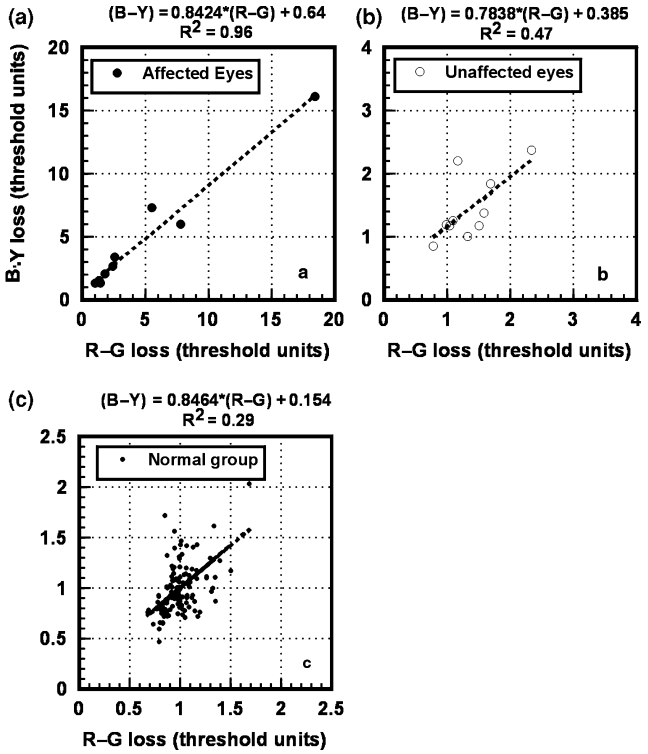

Figure 5. Red-green (RG) and yellow-blue (YB) chromatic thresholds were computed respectively from the major and minor axes of ellipses shown in *Figure 4* and expressed in units that indicate the deviation from the averaged standard CAD observer. Thresholds less than one reveal chromatic sensitivity better than the average normal trichromat whilst thresholds greater than one indicate loss of chromatic sensitivity. The good correlation observed in the affected eyes implies that both RG and YB axes are affected to a similar extent after optic neuritis (graph a). A moderately good correlation is also obtained for the unaffected eyes (graph b). As expected, the correlation is reduced in the normal group as a result of inter-subject variability (graph c). Similar correlation coefficients were obtained when using CIE units instead of threshold units. The correlation coefficient for the affected eyes decreased only from 0.96 to 0.84 when a patient with severe colour vision loss (i.e. >15 normal threshold units) was excluded from the analysis.

the pupil response can be used as an objective independent estimator of damage to the optic nerve and highlights the importance of testing specifically for different functional roles when assessing damage caused by lesions to the optic nerve. Pupil tests can be particularly useful in cases of mild nerve lesions or after a period of recovery when patients showing normal visual acuity or visual fields may still complain of impaired vision.

Several other studies have reported a poor correlation between visual and pupillary deficits in lesions affecting the optic nerve (Kardon *et al.*, 1993; Barbur *et al.*, 2000). Demyelinating neuritis and the relative sparing in pupil function is also often observed during Leber's hereditary optic neuropathy (Bremner *et al.*, 1999; Bose *et al.*, 2005). The lack of correlation between pupil function and visual performance (i.e. colour vision, visual acuity and threshold perimetry) may reflect the fact that retinal ganglion cells mediating the pupil response are morphologically different from those mediating visual function (Perry and Cowey, 1984) and therefore susceptible to differential damage during compression or demyelination of the optic nerve axon fibres.

Assessment of the relapsing and remitting phases during demyelination

The pupil data also reveal that the deficit in the pupil colour response (PCR) is generally larger than that in the pupil light response (PLR) during active phases of demyelination (e.g. recurrent MS) or when recovery is not yet complete; whereas persisting pupil light response (PLR) deficits are more common when visual function improves. Indeed, patients with abnormal visual acuity (worse than 6/6) generally showed larger PCR deficits (6 cases out of 8 in *Figure 3*), whereas patients with recovered visual acuity (6/6 or 6/5) generally showed larger PLR deficits (4 patients out of 6 in *Figure 3*). This finding is also consistent with a previous study (Barbur *et al.*, 2004c) in which the PCR was virtually absent in all patients during the acute phase and PCR deficits were predominant in both the acute phase and within the first 10 weeks of the recovery phase.

In addition, four of the five patients with MS (*Figure 3*) showed a greater deficit in the PCR compared to the PLR. This result was not entirely unexpected since it is known that chromatic vision is affected to a greater extent than achromatic vision in MS patients, as has been reported in numerous electrophysiological, neuroimaging and post-mortem studies (Mullen and Plant, 1986; Russell *et al.*, 1991; Evangelou *et al.*, 2001; Sartucci *et al.*, 2001). Colour vision is also known to be particularly degraded in MS (Flanagan and Zele, 2004; Flanagan and Markulev, 2005; see also *Figure 4*).

The evidence emerging from these studies suggests that, during active phases of demyelination (i.e. during the acute phase or within the first weeks of initial attack or in recurrent MS), colour vision, and in particular the pupil colour response may be more affected than achromatic vision. In contrast, during the recovery phase when visual function improves, PCR deficits are reduced possibly due to spontaneous remyelination (Murray *et al.*, 2001), whereas PLR deficits persist as a consequence of irreversible axonal loss rather than active phases of demyelination. A recent study has emphasized the role of axonal loss rather than demyelination in determining residual disability (Trapp *et al.*, 1998).

The most common type of MS is characterised by a relapsing and remitting course. It would be therefore interesting to study a larger group of MS patients over an extended follow-up period as our data indicate that both chromatic and achromatic measures of visual performance and pupil response sensitivity can provide useful information when assessing damage to the optic nerve during demyelination.

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