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RESEARCH ARTICLE

# Human vision with a lesion of the parvocellular pathway: an optic neuritis model for selective contrast sensitivity deficits with severe loss of midget ganglion cell function

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**Abstract** Achromatic visual function in primates is distributed between two pathways from retina to cortex, the parvocellular and the magnocellular. The relative contribution of these to human achromatic vision is controversial and largely unknown. Here, we use an optic neuritis (ON) model to investigate the effects of a severe loss of parvocellular function on human contrast sensitivity. In our first experiment, we use Gabor stimuli (0.5 cpd, 2 Hz) to show that, compared to normal control eyes, ON causes selective deficits in the two chromatic, cone opponent pathways, with L/M cone opponency affected more than S cone opponency, and a relative sparing of achromatic function. Since L/M cone opponency is carried exclusively by the midget ganglion cells of the parvocellular pathway, this demonstrates a selective deficit of parvocellular function. In a second experiment, we report on two subjects who have lost all L/M cone opponent response in both eyes, indicating a severe loss of parvocellular function. We measure the spatial and temporal contrast sensitivity functions of their remaining achromatic vision, compared with a normal control group, to determine the selectivity of the visual deficit caused by the differential parvocellular loss, and assess the relative contributions of the parvocellular and magnocellular pathways to achromatic contrast sensitivity. We find that parvocellular function contributes selectively at mid- to high spatial frequencies (at low temporal frequencies), whereas magnocellular function determines contrast sensitivity over a very broad temporal frequency range (at low spatial frequencies). Our data bear a striking resemblance to results obtained from primate parvocellular lesions.

**Keywords** Parvocellular · Magnocellular · Optic neuritis · Contrast sensitivity · Color vision · L/M cone opponency · Spatial frequency · Temporal frequency · Retina · LGN

**Abbreviations**

| | |
|---|---|
| ON | Optic neuritis |
| MS | Multiple sclerosis |
| L, M and S cones | Long, medium and short wavelength sensitive cones |
| P-cells | Parvocellular cells |
| M-Cells | Magnocellular cells |
| K-cells | Koniocellular cells |
| LGN | Lateral geniculate nucleus of the thalamus |
| Ach | Achromatic |
| RG | Red-Green |
| BY | Blue-Yellow |
| CPD | Cycles per degree |
| AE | Affected eye |
| FE | Unaffected fellow eye |
| NC | Normal controls |

## Introduction

There are three distinct pathways within the primate subcortical visual system that are broadly selective for different aspects of the visual scene. The parvocellular pathway has by far the largest neural population, composed mostly of retinal midget ganglion cells projecting to the

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P-cell layers of the LGN. This pathway is thought to form the basis of red-green color vision because it has L/M cone opponency with a high sensitivity to red-green color contrast (Lee et al. 1990; Derrington et al. 1984; Dacey 1993a, 2000), and lesions of the parvocellular pathway in primates produce a large reduction in color sensitivity (Merigan et al. 1991; Schiller and Logothetis 1990; Eskin and Merigan 1986; Merigan 1989). Both the midget retinal ganglion cells and the P-cells of the LGN also respond to achromatic contrast, so performing a "double duty" in transmitting both red-green and achromatic information (Lennie and Movshon 2005). The magnocellular pathway is composed of the parasol ganglion cells of the retina projecting to the M-cell layers of the LGN, cell types that are fast-conducting, have large dendritic fields and are much less numerous than cells of the parvocellular pathway. The magnocellular pathway is primarily achromatic with high contrast gain and is sensitive to a wide range of temporal frequencies (Solomon et al. 1999; Kaplan and Shapley 1982; Lee et al. 1990; Derrington and Lennie 1984). Relatively recently, a third, distinct pathway specialized for S cone opponency, the basis of blue-yellow color vision, has been recognized, originating from a population of sparse, specialized retinal bipolar and ganglion cells and projecting with slow conduction velocities to the koniocellular layers of the LGN (Chatterjee and Callaway 2003; Dacey and Packer 2003; Martin et al. 1997; Dacey 1993b). Although many more different ganglion cell types than those mentioned above have been identified morphologically, whose roles are presently being unraveled (Callaway 2005; Dacey 2000, 2004; Rodieck and Watanabe 1993; Masland 2001), it is thought that visual perception is dominated by these three pathways. Although the physiological properties of the single cells that make up these pathways are well documented from primate experiments, their contributions as a whole to different visual functions, especially in human vision, are less well understood. One important outstanding problem is that single cell data from primates show that cells in both the magnocellular and parvocellular pathways respond to achromatic contrast, but the relative contributions of these two pathways as a whole to human achromatic vision remain controversial and undefined.

Optic neuritis (ON) is the term for an inflammatory optic neuropathy caused by a demyelinating disease in the optic nerve, such as multiple sclerosis (MS). An acute episode of visual loss is followed by a slower recovery phase, with a permanent visual deficit frequently remaining (Baier et al. 2005; Hess and Plant 1986a, b). Many investigations have attempted to determine whether there are differential spatial, temporal or chromatic visual losses in ON, detailed further in the Discussion (Dain et al. 1990; Flanagan and Markulev 2005; Flanagan and Zele 2004; Grigsby et al. 1991; Mullen and Plant 1986; Russell et al. 1991; Schneck and Haegerstrom-Portnoy 1997; Travis and Thompson 1989; Trobe et al. 1996; Alvarez and King-Smith 1984; Hess and Plant 1986a, b; Fallowfield and Krauskopf 1984). In this paper, our first aim is to determine whether optic neuritis causes differential deficits in the three post-receptoral pathways described above. While this has been addressed in previous studies, results have been both conflicting and limited by the methods used. We aim to overcome these previous limitations in three ways. First, we use a calibrated cone contrast color space, which allows stimuli to be used that isolate the achromatic, L/M cone opponent and S cone opponent post-receptoral systems and allows a direct comparison of their contrast sensitivities using a biological metric, as that of cone contrast. Many earlier studies used arbitrary color spaces based on the phosphors of the display system, or standard paper-based color vision tests, which do not isolate post-receptoral mechanisms or allow direct threshold comparisons (Dain et al. 1990; Grigsby et al. 1991; Schneck and Haegerstrom-Portnoy 1997). In addition, few previous studies have compared thresholds in the L/M and S cone opponent systems. Second, we make our comparisons using the same visual stimuli to avoid confounding effects arising from variations in the visual deficit across the visual field, or for different spatial or temporal frequencies. We select a low spatial and temporal frequency in order to allow both color and achromatic contrast sensitivity to be measured under the same stimulus conditions (Mullen 1985). Third, we use normal controls as well as unaffected fellow eyes for our comparisons, potentially allowing for more sensitive comparisons than using the fellow eye as a control. We find across a population of 17 eyes that, when compared to normal control eyes, there are significant deficits for both cone opponent pathways, with L/M cone opponency (parvocellular pathway) affected more than S cone opponency (koniocellular pathway), but the achromatic function is relatively spared.

Our second aim is to investigate the spatio-temporal contrast sensitivity of two subjects who were unable to detect the L/M cone opponent stimuli even at their highest contrast, indicating a severe loss of the midget ganglion cells and LGN parvocellular function. These subjects provide a unique opportunity to investigate human achromatic vision in the effective absence of P-cell function and to determine the relative contributions of the magnocellular and parvocellular pathways to human achromatic contrast sensitivity. Some argue that M-cells make the major contribution to human achromatic contrast sensitivity and are not just confined to the detection of fast flicker and motion (Lee et al. 1988, 1990; Lee 2011; Lee and Sun 2009). Others argue that although the small size and dense coverage of P-cells make them likely candidates for supporting

spatial resolution, they have a more extensive role in contrast sensitivity (Lennie and Movshon 2005; Lennie 1993, 1998). We measured the complete spatial and temporal contrast sensitivity functions of the preserved vision of these two subjects and made comparisons with a normal control group to determine any selective deficit caused by the loss of P-cell function and to assess the relative contributions of the parvocellular and magnocellular pathways to human contrast sensitivity. We find that the magnocellular pathway determines contrast sensitivity over a broad temporal frequency range, with parvocellular function contributing at mid- to high spatial frequencies.

## Methods

### Apparatus

Stimuli were displayed on a CRT color monitor (Mitsubishi Diamond Pro 2070SB, resolution of 1,024 × 768 and a frame rate of 120 Hz) connected to a graphics card (Cambridge Research Systems, VSG 2/5) in a generic PC. This graphics card has more than 14 bits of contrast resolution and is specialized for the measurement of visual thresholds. The gamma nonlinearity of the luminance output of the monitor guns was corrected in look-up tables using a Cambridge Research Systems OptiCal photometer. The spectral outputs of the red, green and blue phosphors of the monitor were calibrated using a PhotoResearch PR-645 SpectraScan spectroradiometer. The CIE-1931 chromaticity coordinates of the red, green and blue phosphors were ($x = 0.631$, $y = 0.340$), ($x = 0.299$, $y = 0.611$) and ($x = 0.147$, $y = 0.073$), respectively. The background was gray with a mean luminance of 46.1 cd/m$^2$ at the screen center. The viewing distance was 60 cm from the monitor, and viewing was done in a dimly lit room.

### Observers

We had 15 participants (5 men and 10 women) between the ages of 18 and 75 years and an average age of 44 years. Each participant had clinical histories of confirmed or suspected MS and at least one episode of ON and all were recruited through the MS clinics in Montreal at the Montreal Neurological Institute, the Jewish General Hospital, and the Neuro-Ophthalmology Clinic, the Royal Victoria Hospital. Clinical details are given in Table 1. Of the participants, 13 had a stable residual deficit in one eye that allowed a comparison to be made between the two eyes of each participant, and two patients had documented clinical effects in both eyes. The time between onset of ON and testing varied between 1 and 35 years. None of the participants had an acute episode of visual symptoms or other neurological deficits within the last 8 months prior to testing. None of the participants were diagnosed with any other ophthalmological disorders, and none were on treatment at the time of testing. The diagnosis of ON was confirmed by fundoscopic examination at both the neurology and ophthalmology clinics, revealing a pale optic disk. A review of the family histories revealed no history of color blindness in any of the participants' families. The clinical histories of some of the participants with ON included reports of retro-orbital pain, decreased visual acuity, diplopia and other visual symptoms, but all were asymptomatic at the time of testing. Two of the subjects (GF and NK) undertook more extensive experimental testing. These two subjects also completed the Farnsworth–Munsell 100 hue color vision test in each eye, and both had high error scores in each eye, indicating low color discrimination. The error was distributed across all hues but showed some selectivity for the RG axis.

The experiments were carried out with two types of control groups. Comparisons were made either with the unaffected fellow eyes of each subject or with a control group of normal subjects. Two of our fifteen patients had bilateral ON, and these subjects were excluded from the within group comparisons (13 subjects used) but were included in the between-group comparisons (15 subjects used). Our normal control subjects consisted of 17 trichromatic individuals (10 women and 7 men) with normal or corrected-to-normal vision and normal color vision as tested with the Farnsworth–Munsell 100 hue test. The ages ranged from 21 to 60 years with an average age of 38 years. Of our controls, 10 were used for the second experiment. All observers wore corrective lenses if required. The experiments were performed in accordance with the Declaration of Helsinki, and informed consent was obtained from all the participants.

### Stimuli and color space

Both chromatic and achromatic test stimuli were horizontally oriented Gabor patterns. In the first experiment, the stimuli had a constant spatial frequency of 0.5 cpd and temporal frequency of 2 Hz but varied in color contrast (Ach, RG or BY). This relatively low spatio-temporal frequency maximizes color contrast sensitivity (Kelly 1983; Mullen 1985). In the second experiment, we tested four different spatial frequencies and six different temporal frequencies. The spatial frequencies tested were 0.5, 1, 3 and 10 cpd. All the Gaussian envelopes of the Gabor stimuli were scaled to a fixed space constant of $\sigma = 2$ degrees; hence, even at the lowest spatial frequency, at least 4 stimulus cycles were displayed (i.e., in a patch size of 4 sigma widths). The same visual area was tested for all

**Table 1** Description of each of the 15 subjects

| Subject # and initials | Age | Sex | Initial symptoms | Diagnosis | Afflicted eye | Corrected Snellen acuity | Ishihara plates | Treatment |
|---|---|---|---|---|---|---|---|---|
| *1 NK* | *18* | *M* | *Decreased visual acuity in both eyes a year ago, followed by right-sided hemiparesis* | *MS/ON* | *Both* | *6/6* | *Pass* | *Was on Rebuff and other DMT (Mitoxantrone) Currently on none* |
| 2 CC | 33 | F | Right eye pain and diplopia one year ago, followed by left-limb numbness | MS/ON | Right | 6/6 | Pass | Beta-interferon |
| *3 GF* | *37* | *F* | *Right eye decrease visual acuity and diplopia in 1990. Subsequent episode of ON in 2004 (eye unknown). Other MS symptoms: right-sided hemiparesis, vertigo and others* | *MS/ON* | *Both* | *6/9* | *Pass* | *Currently not on any. Was on steroids and Beta-interferon and mitoxantrone* |
| 4 SR | 37 | F | Right eye pain and decreased vision a few years ago, followed by multiple other symptoms | MS/ON | Right | 6/9 | Unknown | Was on steroids and Beta-interferon |
| 5 WS | 38 | F | Decreased right eye visual acuity 6 years ago<br>Free of symptoms after | CIS/ON | Right | 6/6 | Pass | Received steroids. Not on any DMT |
| 6 SA | 42 | F | Right eye pain and central scotoma 7 years ago, followed by dysarthria | MS/ON | Right | 6/6 | Unknown | Steroids, Beta-interferon |
| 7 WW | 42 | F | Total right eye vision loss, followed by recovery but multiple neurological deficits | MS/ON | Right | 6/6 | Unknown | Steroids and Avonex |
| 8 MG | 44 | F | 2 Episodes of decreased right eye visual acuity. Not clear whether further neurological symptoms followed | CIS/ON | Right | 6/6 | Unknown | Steroids |
| 9 PB | 45 | M | Left eye pain and decreased vision that recovered over several months<br>Not clear whether had more episodes after or any further symptoms | CIS/ON | Left | 6/6 | Unknown | Steroids |
| 10 GU | 48 | F | Vertigo followed by blurred vision and diplopia a year ago | MS/ON | Right | 6/6 | Pass | Steroids planed, not yet on DMT |
| 11 MM | 50 | M | 2 Episodes of right mild vision loss 3–4 months apart | CIS/ON | Right | 6/6 | Pass | Steroids, not clear whether on any DMT |
| 12 CT | 50 | M | Right-sided numbness followed 8 months later by left eye vision loss over 24 h, 5–6 years ago, back to normal within a month | MS/ON | Left | 6/6 | Pass | Steroids and Beta-interferon |
| 13 AS | 53 | M | Sudden onset of left eye pain and blurry vision 8 years ago | MS/ON | Left | 6/6 | Pass | Steroids, not clear whether on any DMT |
| 14 MD | 58 | F | First attack 30 years ago, presented with diplopia | MS/ON | Right | 6/6 | Unknown | Currently not on any treatment |
| 15 NF | 72 | M | Blurry vision 36 years ago, followed up by a few minor episodes of hemiparesis | MS/ON | Left | 6/6 | Pass | Currently not on any. Not known whether patient received steroids during acute attacks |

Patients are ordered by age. Two patients showed optic neuritis (ON) in both eyes and are given in italic. Clinically isolated syndrome (CIS), disease-modifying therapy (DMT), multiple sclerosis (MS). Steroids were only used during acute attacks

stimuli to avoid any confounding effects arising from variations in the visual loss across the visual field. Gabors were sinusoidally phase-reversed in time at six different temporal frequencies: 1, 2, 4, 8, 16 and 32 Hz. All Gabor stimuli were presented in a contrast-modulated temporal Gaussian envelope of $\sigma = 125$ ms.

Stimuli were represented in a three-dimensional cone contrast space (Cole et al. 1993; Eskew et al. 1999;

Sankeralli and Mullen 1996) in which each axis is defined by the incremental stimulus intensity for each cone type to a given stimulus normalized by the respective intensity of the fixed adapting white background. Stimulus chromaticity is given by the vector direction and contrast by vector length within the cone contrast space. Cone excitations for the L, M and S cones were calculated using the cone fundamentals of Smith and Pokorny (1975). A linear transform was calculated to specify the required phosphor contrasts of the monitor for given cone contrasts. Three cardinal stimuli (Ach, BY and RG) were defined within this space to isolate each of the three different post-receptoral mechanisms. The achromatic (Ach) stimulus activates L, M and S cones equally (L, M and S cone weights of 1, 1 and 1, respectively), the S cone opponent (blue-yellow, BY) stimulus activates S cones only (cone weights of 0, 0, 1), and the isoluminant L/M cone opponent (red-green, RG) stimulus activates L and M cones opponently in a proportion determined by the isoluminant point and has no S cone activation (cone weights of $1, -\alpha, 0$, where $\alpha$ is a numerical constant obtained at isoluminance). Stimulus contrast is defined as the root mean square or the vector length in cone contrast units ($Cc$):

$$C_C = \sqrt{(L_C)^2+(M_C)^2+(S_C)^2} \quad (1)$$

where $L_C$, $M_C$ and $S_C$ represent the $L$, $M$ and $S$ Weber cone contrasts (the L, M or S cone response increment or decrement divided by the respective $L$, $M$ or $S$ cone response to the achromatic background). This metric is greater by a factor of $\sqrt{3}$ from the conventional luminance contrast.

For each eye of each observer, the isolation of the red-green mechanism at isoluminance (value of $\alpha$ above) was estimated by a minimum motion task in the cone contrast space (Cavanagh et al. 1984). The minimum motion perceived of the Gabor grating was established using a method of adjustment. A small black fixation point was displayed during the minimum motion task. In each orientation, a minimum of 10 settings were measured per eye. If vision was insufficient to do the task in the affected eye, the settings from the less-affected or unaffected fellow eye were used. Luminance artifacts in chromatic gratings were minimized by the use of a low-spatial-frequency stimulus (0.5 cpd) (Bradley et al. 1992).

### Procedure

We measured contrast detection thresholds for the Gabor stimuli. A two-alternative forced-choice staircase procedure was used with a presentation interval of 1 s per trial, separated by 0.5 s. The subjects indicated in which interval the stimulus appeared (the other was blank). A '2-down, 1-up' weighted staircase was used with audio feedback. A reversal was defined when the subject responded incorrectly after a minimum of two consecutive correct responses. Each staircase terminated after six reversals. For reversals after the first, stimulus contrast was raised by 25% following one incorrect response and lowered by 12.5% following two consecutive correct responses. (For the first reversal, stimulus contrast was raised by 50%.) For a given staircase session, the number of total trials ranged between 35 and 65 trials. The threshold value was calculated as the arithmetic mean of the last five reversals of the staircase. Each plotted threshold is based on the arithmetic mean of a minimum of at least three staircase measurements. Subjects were asked to focus on a small black fixation point in the center of the screen and location of the stimulus that was displayed before and after the stimulus was presented and during the interstimulus intervals. We converted contrast thresholds to decibels, which is equivalent to $20 \times \log(1/\text{contrast threshold})$. We used this logarithmic scale to normalize the differences in contrast sensitivity between the color conditions (RG, BY & Ach) (contrast sensitivity = 1/contrast threshold).

## Results

### Effect of ON on achromatic, L/M cone opponent and S cone opponent thresholds

The aim of this experiment is to compare the effects of ON on the contrast sensitivity of the achromatic and two cone opponent pathways of human vision. This comparison is made using the same stimulus configuration and retinal location for each pathway tested and is made in terms of cone contrast, a biologically based metric that allows direct comparisons of sensitivity between the three different stimuli. Figure 1 shows results for a within-group comparison between affected (AE) and unaffected fellow eyes (FE) in 13 subjects. A 2-way ANOVA showed a significant main effect of eyes: $F(1, 2) = 23.56$, $P < 0.0001$. Bonferroni post-tests revealed a significant difference in contrast sensitivity between affected and unaffected eyes for both red-green ($P < 0.001$) and blue-yellow contrasts ($P < 0.05$), but no difference for achromatic contrasts ($P > 0.05$). The data imply that there is a significant deficit in contrast sensitivity for color contrasts in eyes affected by ON compared to the unaffected eye of the same subject. The proportional difference between affected and unaffected eyes (in decibels) is shown in Fig. 1b and shows a slightly larger deficit for red-green contrast sensitivity compared to blue-yellow contrast sensitivity, which does not reach significance.

In Fig. 2, we make a between-groups comparison of affected eyes versus normal control eyes (NC). All 17 affected eyes are included, including both eyes of the subjects with bilateral optic neuritis. A 2-way ANOVA

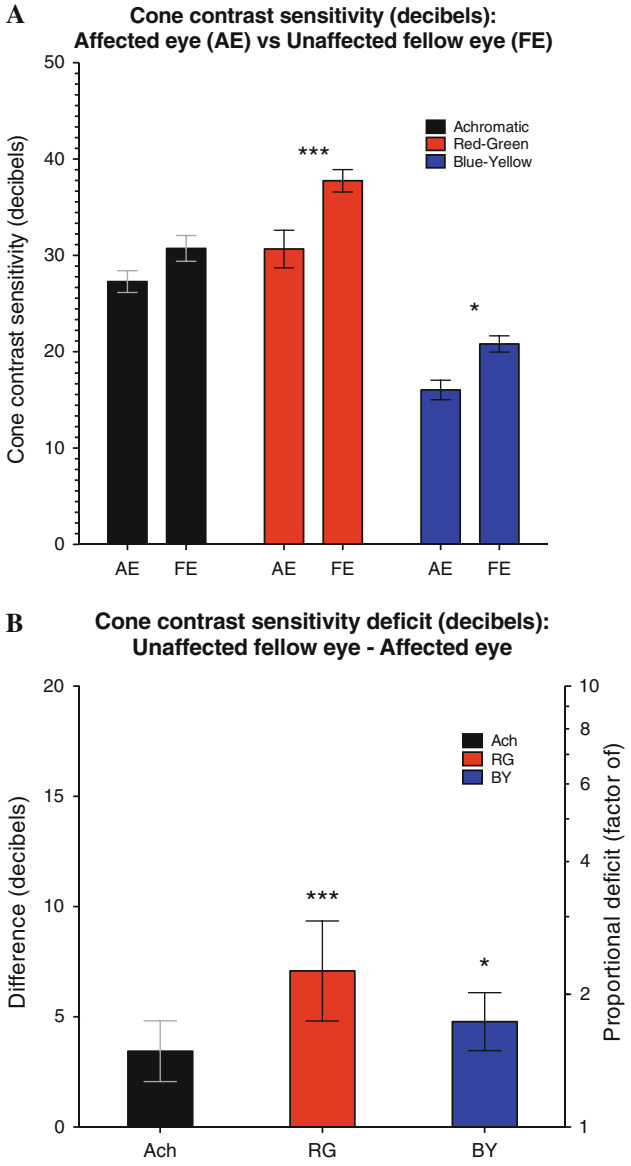



**Fig. 1** Contrast sensitivity in decibels (*dB*) of affected eyes (*AE*) and unaffected fellow eyes (*FE*) for achromatic, *red-green* and *blue-yellow* gratings (dB = 20 × log(contrast sensitivity)). There were 13 subjects with 13 affected eyes, and 13 control eyes ($n = 26$). The *error bars* represent ±SEM. A 2-way ANOVA was run with Bonferroni post-tests, along with a one-tailed *t* test. * Indicates a significant difference at $P < 0.05$, *** indicates a significant difference at $P < 0.001$. **a** A comparison of contrast sensitivity for affected eyes versus unaffected fellow eyes. **b** The proportional difference (in decibels) between unaffected fellow eyes and affected eyes. The *right axis* represents the numerical proportional deficit

revealed a significant main effect of eyes: $F(1, 2) = 46.02$, $P < 0.0001$, indicating a significant difference between the contrast sensitivity of each group. Bonferroni post-tests showed significant differences between groups for both the red-green ($P < 0.001$) and blue-yellow contrasts ($P < 0.001$). There was no significant difference between groups for achromatic contrast sensitivity ($P > 0.05$). This shows that there is a deficit in contrast sensitivity in eyes with ON compared to normal control eyes that is selective for the chromatic stimuli. The proportional difference between affected and normal control eyes (in decibels) is shown in Fig. 2b. A one-tailed *t* test revealed a significantly larger deficit in red-green contrast sensitivity compared to blue-yellow contrast sensitivity ($P = 0.0317$), while a 2-way ANOVA revealed a nearly significant interaction between deficit and color contrast ($F(1,1) = 3.878$, $P = 0.0532$). The one-tailed *t* test was performed because we were only concerned if the deficit in one color contrast was greater than the other ($H_O$: $\mu_{R/G} > \mu_{B/Y}$) and because of a floor effect in the data as 6 of the 17 eyes reached floor levels, making their deficits likely more severe than was shown. These issues could confound a two-tailed *t* test. Together, these results imply a selective deficit for red-green compared to blue-yellow contrasts.

We make a comparison between unaffected fellow eyes and the normal control eyes in Fig. 3. There was no significant effect of eyes as shown by a 2-way ANOVA: $F(1, 2) = 1.062$, $P = 0.3061$. There were no significant differences between any individual contrasts (all $P > 0.05$) as indicated by Bonferroni post-tests. This shows that even though the unaffected fellow eyes have slightly poorer contrast sensitivity for the two chromatic stimuli, there is no significant deficit in contrast sensitivity.

## Achromatic contrast sensitivity in subjects with complete loss of L/M cone opponency

We found that two of our subjects tested (GF and NK) had a complete loss of L/M cone opponency. In these subjects, neither eye could detect the red-green stimulus even at the highest contrast that could be presented on the monitor. Their red-green deficit represents an 11-fold (21 dB) loss from normal red-green sensitivity, compared to a fourfold (12 dB) loss found in the ON group as a whole. Each subject, however, retained sensitivity to the S-cone-isolating (BY) stimuli, with a threefold deficit found in the two subjects tested as well as the ON group as a whole. They also retained achromatic contrast sensitivity as explored in the following experiments. Since L/M cone opponency is carried by the midget ganglion cells of the parvocellular pathway, the absence of any response to red-green contrast indicates that there is a severe loss of parvocellular function in the retinal region of stimulation in these subjects. In this case, the preserved achromatic function reflects the responses of the remaining M-cells, which form the only other pathway with sensitivity to achromatic contrast. The remaining S cone contrast sensitivity reflects the function of the specialized neurons of the retina and koniocellular layers of the LGN, which are selective for S cone opponency and unresponsive to achromatic contrast. Thus, these

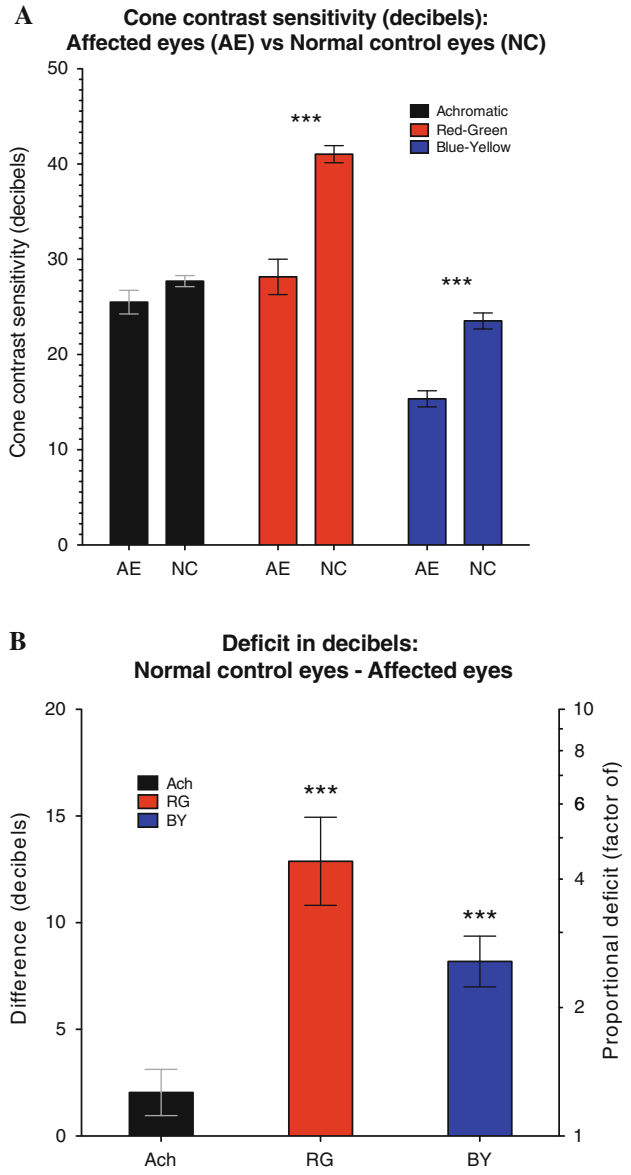



**Fig. 2** Contrast sensitivity in decibels (*dB*) of affected eyes (*AE*) and normal control eyes (*NC*) for achromatic, *red-green* and *blue-yellow* gratings (dB = 20 × log(contrast sensitivity)). There were 13 subjects with 13 affected eyes, and 17 control eyes ($n = 30$). The two subjects with both eyes affected were excluded. The *error bars* represent ±SEM. A 2-way ANOVA was run with Bonferroni post-tests. *** Indicates a significant difference at $P < 0.001$. **a** A comparison of the contrast sensitivity for affected eyes versus normal control eyes. **b** The proportional difference (in decibels) between normal control eyes and affected eyes. The *right axis* represents the numerical proportional deficit

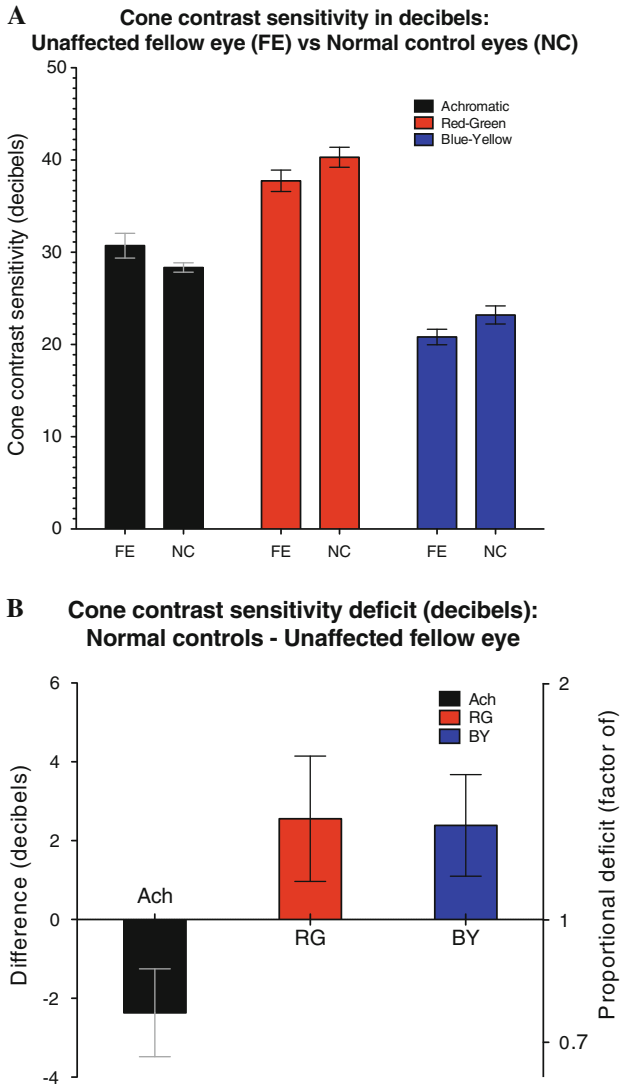
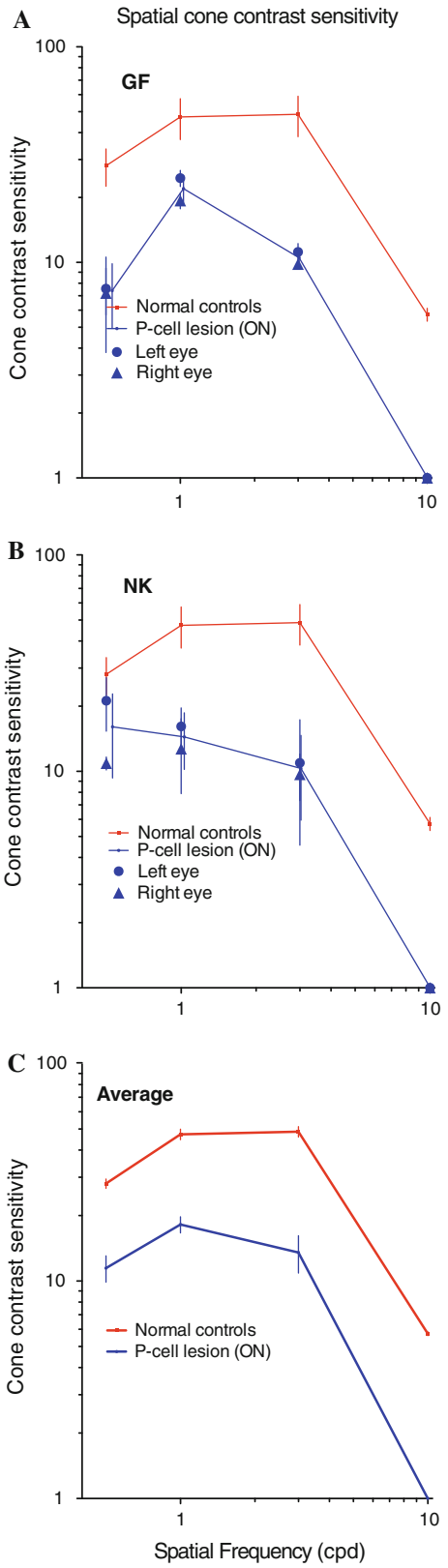



**Fig. 3** Contrast sensitivity in decibels (*dB*) of unaffected fellow eyes and normal control eyes viewing achromatic, *red-green* and *blue-yellow* gratings (dB = 20 × log(contrast sensitivity)). There were 13 subjects with 13 affected eyes, and 13 control eyes ($n = 26$). The *error bars* represent ±SEM. A 2-way ANOVA was run with Bonferroni post-tests. **a** A comparison of contrast sensitivity for unaffected fellow eyes versus normal control eyes. **b** The proportional difference (in decibels) between normal control eyes and unaffected fellow eyes. The *right axis* represents the numerical proportional deficit. Unaffected fellow eye (*FE*), Normal control eyes (*NC*)

two subjects provide a unique opportunity to investigate the remaining magnocellular function in the effective absence of paracellular function.

We measured the achromatic spatial and temporal contrast sensitivity functions in the 4 eyes of these two subjects and compared them with those for normal control eyes. Results for spatial contrast sensitivity (measured at 2 Hz) are shown in Fig. 4 for each eye of each subject and the control group, with their averages. Results for the temporal contrast sensitivity (measured at a spatial frequency of 0.5 cpd) are shown in Fig. 5 using the same format. The proportional deficits between the normal and 4 affected eyes are plotted as a function of spatial and temporal frequency in Fig. 6a, b, respectively. For the spatial deficit (Fig. 4), statistical comparisons based on the ten control eyes and four affected eyes show that there is a significant deficit between affected and control eyes (2-way ANOVA: $F(1,3) = 241.2$,




◀ **Fig. 4** Achromatic contrast sensitivity as a function of spatial frequency, at a temporal frequency of 2 Hz. The *red* in *all panels* represents the average of 10 normal control eyes. The *blue line* represents the average of the two eyes for each of two patients, GF (*top panel*), and NK (*middle panel*). The *circles* are the contrast sensitivity of the left eye, and the *squares* are the contrast sensitivity of the right eye. The *bottom panel* shows averaged results for all 4 eyes (*blue line*). *Error bars* represent ±SEM

$P < 0.0001$). There is also an interaction between spatial frequency and affected versus normal control eyes (2-way ANOVA: $F(3,3) = 22.66$, $P < 0.0001$), indicating that the contrast sensitivity deficit depends significantly on the spatial frequency used. The plot in Fig. 6a clearly shows that the deficit increases steeply as a function of spatial frequency from 1 to 10 cpd, with complete loss of sensitivity by 10 cpd and the loss ranging from 2.4- to 5.7-fold. The slope of the line of best fit ($m = 0.343$) varied significantly from a slope of zero ($P = 0.0048$). This indicates that the selective and severe loss of parvocellular over magnocellular function in the central region of the visual field has resulted in a selective loss of the mid- and higher spatial frequencies (starting above 1 cpd).

For the deficit in temporal contrast sensitivity (Fig. 5), statistical comparisons show that there is a significant deficit between affected and control eyes (2-way ANOVA: $F(3,3) = 22.66$, $P < 0.0001$). There is no significant trend in the difference between contrast sensitivity as a function of temporal frequency (Fig. 6b); the slope of the line of best fit is not significantly different from zero ($m = 0.021$, $P = 0.193$). This indicates that the loss of contrast sensitivity is not selective for temporal frequency over the range that we have measured.

The dashed lines (Fig. 6) show the results of a primate lesion study in which retinal midget ganglion cell function was abolished in macaques by the use of neurotoxin, acrylamide, and the loss of contrast sensitivity was measured (Merigan and Eskin 1986; Figs. 3, 4). The primate results have been plotted directly without any normalization. Primate and human data are in close agreement in terms of the selectivity of the loss. Like the human loss, the primate loss increases steeply for spatial frequencies above 1 cpd. Across temporal frequency, the primate loss is unselective and virtually absent, resembling the human data; however, the human deficit is larger than in the primate, supporting the idea that ON has produced an overall but unselective reduction in magnocellular sensitivity.

## Discussion

### Cone contrast sensitivity of the L/M cone opponent, S cone opponent and achromatic pathways in optic neuritis

In our first experiment, we compared the effect of optic neuritis on the contrast sensitivities of the L/M cone

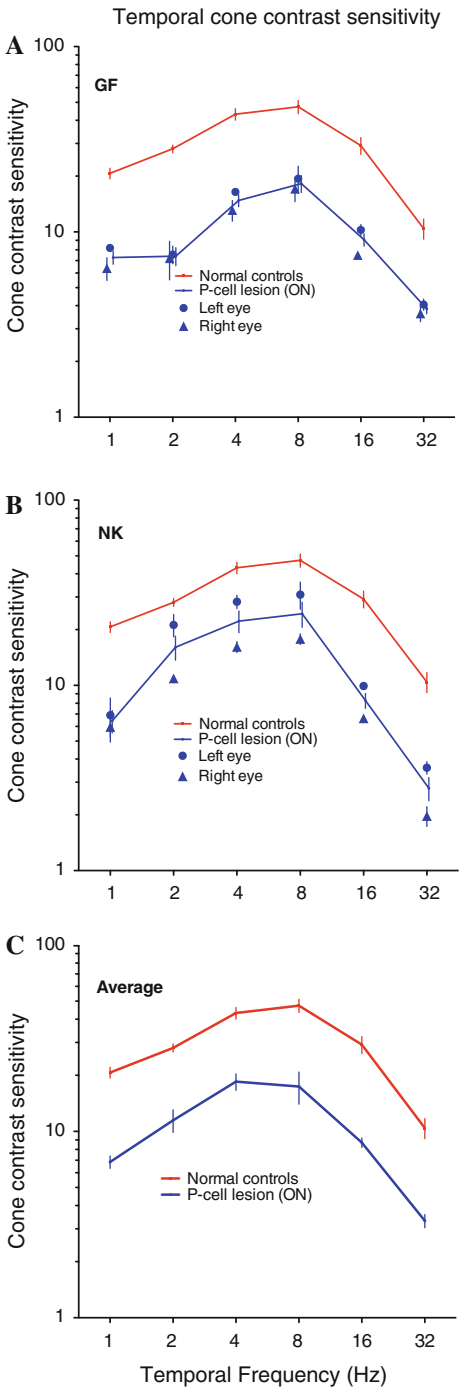



**Fig. 5** Achromatic contrast sensitivity as a function of temporal frequency, at a spatial frequency of 0.5 cpd. The *red line* in both figures represents the average of 10 normal control eyes. The *blue line* represents the average of the two eyes for each of the patients, GF (*top panel*) and NK (*middle panel*). The *circles* are the contrast sensitivity of the left eye, and the *squares* are the contrast sensitivity of the right eye. The *bottom panel* shows averaged results for all 4 eyes (*blue line*). *Error bars* represent ±SEM

opponent, S cone opponent and achromatic post-receptoral pathways. It is interesting that neither of the comparisons with the control groups (unaffected fellow eyes of each subject and age-matched normal controls) showed any significant deficit in achromatic contrast sensitivity, which was close to normal for the stimulus conditions we tested (low spatial and temporal frequency modulation). Both the two chromatic pathways, however, had significant deficits, which were greatest for the comparisons with the normal control group for reasons discussed below. In addition, the difference between the two cone opponent responses was significant for comparisons with the normal control group, indicating a selectively greater deficit on average for the L/M cone opponent response.

In general, comparisons with the normal control group reveal greater deficits than comparisons with the clinically unaffected eyes, and this is likely due to the better sensitivity of normal eyes compared to unaffected fellow eyes (although this effect did not reach significance), and the inclusion of 4 additional affected eyes (of 2 subjects) in comparisons with the normal control group, which were excluded from the between-eye comparison because the fellow eyes were not clinically normal. In summary, we find a significant selective deficit in the L/M cone opponent pathway, followed by a smaller but still significant deficit in the S cone opponent response, with a weak, insignificant effect for achromatic contrast sensitivity. We note that this selective loss of L/M opponency is not "carried" by a few individuals in the group. A proportion of eyes (6/17) in the group reached a floor effect in their L/M cone opponent sensitivity, since they were unable to see the stimulus even at the highest contrast available, which will compress (shrink) the L/M opponent deficit. A selective loss of L/M cone opponency indicates a selective loss of P-cell function, originating in the ganglion cell axons, with axonal injury arising as a consequence of the initial demyelinating, inflammatory attack. A permanent visual deficit in ON is likely to signify that there is Wallerian degeneration and axonal damage, resulting in thinning of the optic nerve (atrophy) and possible loss of retinal ganglion cells. It is well accepted that the smaller axons of the midget ganglion cells are likely to be the most severely affected (Tansey et al. 1985). Clearly, however, the effects include other axons as we also find a significant loss of S cone opponency, which is thought to be carried by a different population of relatively small, slowly conducting axons.

Although Köllner (1912) first suggested that red-green color vision deficits are characteristic of optic nerve disease, his observations were based on color appearance and color naming. Subsequent detailed measurements of color appearance revealed inconsistent support for Köllner's classification (Mullen and Plant 1987). This is not surprising as the chromatic pathways of the optic nerve are cone opponent and have no direct relationship with color appearance or color names, which are established at a higher, cortical level. More modern approaches, which

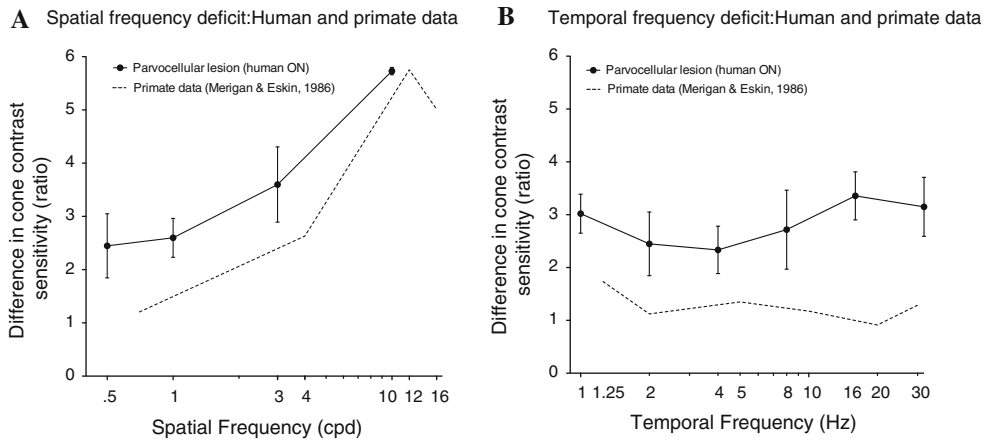



**Fig. 6** **a** Proportional loss in contrast sensitivity, plotted as the ratio of average contrast sensitivities for the normal control eyes to the 4 P-cell lesioned eyes, plotted in **a** as a function of spatial frequency at a constant temporal frequency (2 Hz) and in **b** as a function of temporal frequency at a constant spatial frequency (0.5 cpd). In **a**, the slope of the best-fitting line varied significantly from 0 ($P = 0.0048$), indicating that there is a selective deficit in contrast sensitivity with increase in spatial frequency. In **b**, the slope of the best fitting line did not vary significantly from 0 ($P = 0.1963$), indicating no selective deficit for any temporal frequency. For comparison, the *dashed lines* show the contrast sensitivity deficit for primates with a parvocellular lesion produced by the neurochemical ablation of midget ganglion cells, taken from Merigan & Eskin (1986) and plotted using the same scale (i.e., not normalized)

measure thresholds and separate the chromatic and achromatic responses, have come up with mixed results. Some have measured sensitivities to isoluminant and achromatic Gaussian blobs or gratings and reported a larger deficit for chromatic thresholds with achromatic thresholds relatively spared (Fallowfield and Krauskopf 1984; Mullen and Plant 1986). While others (Dain et al. 1990; Russell et al. 1991) compared chromatic and achromatic thresholds and found no selective loss, however, these comparisons were made for different stimulus arrangements for chromatic and achromatic stimuli. Grigsby et al. (1991) and Travis and Thompson (1989) report a chromatic loss but made no direct comparison with achromatic responses. One other group, which separated the two cone opponent axes, using a matrix of checks, also reports selective L/M cone opponent deficits over S cone opponent (Flanagan and Markulev 2005; Flanagan and Zele 2004), as we do here, while others found no selective loss for L/M over S cone opponency (Fallowfield and Krauskopf 1984).

## Achromatic contrast sensitivity with severe loss of P-cell function

Two of our subjects had no measurable L/M cone opponency in either eye, indicting a very severe loss of P-cell function within the visual area tested. Moreover, since P-cells are highly sensitive to RG contrast, considerably more than to achromatic contrast, the absence of any measureable RG chromatic response is a sensitive indicator that P-cell function is so severely impaired as to be effectively eliminated. Retinal midget ganglion cells and LGN P-cells have a dual role in vision, responding to both RG color contrast and achromatic contrast (Lee et al. 1990; Derrington and Lennie 1984), while retinal parasol ganglion cells and LGN M-cells are primarily achromatic with little chromatic response. The relative contributions to human achromatic contrast sensitivity of these magnocellular and parvocellular pathways are highly controversial and presently unknown. Much of the evidence has been based on the properties of individual primate cells, with some arguing that M-cells make the major contribution to achromatic contrast, based on their high contrast sensitivity compared to P-cells and their spectral properties (Lee et al. 1988, 1990; Lee 2011; Derrington and Lennie 1984), while others argue for a significant contribution of P-cells, due to their overwhelmingly greater population size (Lennie and Movshon 2005; Merigan and Maunsell 1993). These relative contributions have been very challenging to unravel, as the functional response of a large cell population is not easily predicted from the properties of single cells. Data have so far only been available in nonhuman primates.

We have explored the preserved vision in these two subjects as a way of assessing the relative contributions of the magnocellular and parvocellular pathways to achromatic vision. Given the severe loss of parvocellular function in these two subjects, the shapes of their achromatic spatial and temporal contrast sensitivity functions are likely to reflect the function of their remaining magnocellular pathways. This remaining vision, however, may also include a general sensitivity deficit due to the likely effects of ON on the M-cell population. We therefore use a differential loss of contrast sensitivity confined to a particular

band of spatial or temporal frequencies compared to normal controls to indicate the selective contribution of parvocellular function to normal vision. In both eyes of both subjects, we found a selective loss of sensitivity in the spatial contrast sensitivity function (Fig. 6a) confined to the mid- and high spatial frequencies, with the data suggesting that spatial frequencies between 1 and 10 cpd have a parvocellular contribution and above 10 cpd are entirely mediated by parvocellular function (at the temporal frequency used of 2 Hz). We note these results are compatible with a previous study of ON, which have reported a significant correlation between chromatic losses and losses in high spatial frequencies (Grigsby et al. 1991) but are inconsistent with another study, which reported a lack of correlation (Dain et al. 1990). The shape of the temporal contrast sensitivity function, however, showed no selective losses, suggesting that M-cells determine thresholds over a very broad range of temporal frequencies (1–32 Hz), for the relatively low spatial frequency used of 0.5 cpd. The relatively small overall reduction across the range of temporal frequencies tested suggests that there is some effect on magnocellular function.

Our result bare a striking resemblance to psychophysical results obtained from primates after lesions of the midget ganglion cell population. Midget retinal ganglion cells in primates can be severely and selectively depleted with acrylamide injections (Eskin et al. 1985; Merigan et al. 1985; Merigan and Eskin 1986), or the parvocellular pathway can be lesioned directly in a localized part of the visual field with ibotinic acid in the LGN (Merigan et al. 1991; Merigan and Maunsell 1990). After a severe lesion of the parvocellular pathway, macaque primates show a fourfold loss in spatial resolution (Merigan and Eskin 1986). This is very similar to the losses that we find in our two subjects with severe parvocellular deficits. Direct comparisons between our data and data for primates with retinal midget ganglion cell lesions (Merigan and Eskin 1986) show a strong resemblance between the two data sets (Fig. 6). A role for the parvocellular pathway in visual acuity is compatible with the known physiology of primate midget ganglion cells and LGN P-cells, which have small receptive fields and very dense coverage (Lankheet et al. 1998). Here, we suggest that the parvocellular contribution to human contrast sensitivity extends to spatial frequencies well below the resolution point, contributing to contrast sensitivity between 1 and 10 cpd and entirely supporting resolution above 10 cpd. The selective contribution of the parvocellular pathway to the high spatial frequency but temporally slow 'corner' of the contrast sensitivity function that we find in human vision is thus very consistent with the results of primate lesion studies.

The contribution of magnocellular function over a broad range of temporal frequencies including low temporal frequencies down to 1–2 Hz is surprising. Since parasol ganglion cells and LGN M-cells are the main contributors to the dorsal pathway, which supports motion and flicker perception (Maunsell et al. 1990), they have come to be associated with the perception of high temporal frequencies, an association supported by their fast conduction velocities and good temporal resolution (Derrington and Lennie 1984; Lee et al. 1990). Our results suggest they make a contribution to contrast sensitivity over a much broader range of temporal frequencies. These results are compatible with physiological data showing that retinal LGN M-cell responses are maintained over a wide range of temporal frequencies (Levitt et al. 2001; Lee et al. 1990; Derrington and Lennie 1984), making them candidates for a more extensive role in vision. We note that Merigan et al. (1991) have indicated a parvocellular contribution for static stimuli, which we did not test, as our lowest temporal rate was 1 Hz. Our results suggest that the magnocellular pathway does not just support the dorsal pathway functions of flicker and motion perception but also contribute significantly to the ventral pathway functions at much slower temporal rates. This is also supported by the known contributions of M-cells to extrastriate ventral areas (Ferrera et al. 1994). Since the contrast sensitivity of M-cells is considerably higher than that of P-cells (Sclar et al. 1990), they may make a disproportionately greater contribution to contrast sensitivity as opposed to suprathreshold tasks. This remains to be explored further. Overall, it is surprising how much vision these subjects retain, given that their parvocellular lesion is likely to have eliminated about 70% of retinal neuron function in the regions of visual field affected, and indicates an important role of M-cells despite their low population density.

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