Functional Loss in the Magnocellular and Parvocellular Pathways in Patients with Optic Neuritis

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Purpose. To evaluate contrast threshold and contrast gain in patients with optic neuritis under conditions designed to favor mediation by either the inferred magnocellular (MC) or parvocellular (PC) pathway.

Methods. Achromatic and chromatic contrast discrimination was measured in 11 patients with unilateral or bilateral optic neuritis and in 18 age-matched controls with normal vision, using achromatic steady- and pulsed-pedestal paradigms to bias performance toward the MC or PC pathway, respectively. In addition, L-M chromatic discrimination at equiluminance was evaluated using the steady-pedestal paradigm. A physiologically plausible model could describe the data with parameters accounting for contrast gain and contrast sensitivity in the inferred MC or PC pathway. The fitted parameters from the eye affected by optic neuritis were compared with those from the normal eye using generalized estimation equation (GEE) models that can account for within-subject correlations.

Results. Compared with normal eyes, the affected eyes had significantly higher saturation parameters when measured with both the achromatic pulsed-pedestal paradigm (GEE: β [SE] = 0.35 [0.06]; $P < 0.001$) and the chromatic discrimination paradigm (β [SE] = 0.18 [0.08]; $P = 0.015$), suggesting that contrast gain in the inferred PC pathway is reduced; the affected eyes also had reduced absolute sensitivity in the inferred MC pathway measured with the achromatic steady-pedestal paradigm (β [SE] = 0.12 [0.04]; $P = 0.005$).

Conclusions. Optic neuritis produced large sensitivity losses mediated by the MC pathway and contrast gain losses in the inferred PC pathway. A clinical framework is presented for interpreting contrast sensitivity and gain loss to chromatic and achromatic stimuli in terms of retinal and postretinogeniculate loci contributions to detection and discrimination. (*Invest Ophthalmol Vis Sci.* 2011;52:8900–8907) DOI:10.1167/iovs.11-7644

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Optic neuritis refers to an inflammation of one or both optic nerves that is painful and results in temporary loss or blurring of vision. Vision typically recovers gradually when assessed with conventional clinical methods. Sensitive psychophysical approaches, however, often reveal a long-lasting loss in spatial, temporal, luminance, and/or chromatic visual function.[1–15] It is still to be determined how the reported luminance and chromatic sensitivity losses in optic neuritis reflect deficits in retinogeniculate and/or cortical function.

Modern anatomic and physiological studies have identified three major neural retinogeniculate pathways in the primate visual system that convey retinal information to the visual cortex, that is, the magnocellular (MC), parvocellular (PC), and koniocellular (KC) pathways.[16,17] These parallel pathways have distinctive temporal, spatial, chromatic, and contrast response characteristics and mediate different aspects of vision.[18,19] The MC pathway sums signals from L- and M-cones,[20–22] with receptive fields showing either on- or off-center organization. The MC pathway, because of its band-pass spatiotemporal characteristic with high temporal frequency sensitivity, is considered to have an important role in detecting contrast over a wide range of luminances[23] and in providing input to higher order pattern and motion processes.[24] The PC pathway, on the other hand, is thought to have primary roles in chromatic processing and visual acuity and to provide input to higher-order pattern processes.[25] In PC pathway cells, spectral opponency to lights of various spectral composition is obtained by differencing of L- and M-cone signals.[20] On- and off-center receptive field organization reveals four subtypes of PC pathway cells. PC pathway cells have a low-pass spatiotemporal characteristic to chromatic stimuli and a band-pass spatiotemporal characteristic to achromatic stimuli. The achromatic temporal modulation transfer functions of PC pathway cells show a lower cutoff frequency than do MC pathway cells.[26,27] The KC pathway differences S-cone signals from the sum of the L- and M-cones, with the small bistratified ganglion cells[28] responding to increases in S-cone signal in the center or decreases in (L+M) in the surround. The KC pathway, thought to underlie blue-yellow chromatic discrimination,[29] was not evaluated in this study.

Typical clinical findings in optic neuritis include loss of visual acuity and color vision, two visual functions thought to be mediated by the PC pathway.[17] The PC pathway accounts for approximately 80% of optic nerve fibers,[30] and there is considerable interest in determining whether the visual deficit in optic neuritis occurs selectively in the thinly myelinated ganglion cells of the PC pathway. Numerous attempts have been made to separate PC- and MC-mediated vision by taking advantage of different functional properties of the two pathways. The MC pathway shows greater sensitivity to lower spatial frequencies, higher temporal frequencies, and achromatic targets; the PC pathway shows greater sensitivity to higher spatial frequencies, lower temporal frequencies, and chromatic stimuli.[3–15] Typically, re-

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duced chromatic or luminance sensitivity has been interpreted as PC or MC deficits, respectively, and it has been reported that the visual deficit in optic neuritis is greater in the PC pathway than in the MC pathway.[9] This interpretation is precarious since the PC ganglion cell responds well to achromatic stimuli.[18] Further, different metrics used for achromatic and chromatic stimuli make the direct comparison of visual performance between the inferred PC and MC deficits difficult. In the present study, we addressed two outstanding questions in the study of luminance and chromatic sensitivity losses in optic neuritis by using an experimental approach that measures the sensitivity of both pathways to the same spatiotemporal stimuli, a necessary requirement for interpreting the relative sensitivity losses in the two pathways. First, we sought to determine achromatic contrast sensitivity in both the PC and MC pathways. Second, we wanted to measure PC pathway achromatic and chromatic contrast gain responses.

In this study, we investigated MC and PC deficits in optic neuritis using a set of psychophysical paradigms developed by Pokorny and Smith[31] to separate MC and PC pathway contrast discrimination on the basis of differential contrast response characteristics of primate MC and PC cells. MC cells show response saturation to luminance contrast, whereas the PC cells' responses are relatively linear, and MC cells have much greater contrast gain than PC cells.[32] The PC chromatic contrast gain is intermediate between the achromatic MC and PC contrast gains.[33] Unlike stimulus paradigms used in previous studies, these paradigms measure the responses of the two pathways by using identical stimuli that differ only before and after adaptation. We used two psychophysical paradigms: the pulsed-pedestal paradigm, to reveal PC contrast gain, and the steady-pedestal paradigm, to evaluate steady state MC pathway sensitivity. The rationale for the paradigms revealing MC or PC mediation are fully explained elsewhere.[31,33–35] Briefly, PC mediation of the pulsed-pedestal thresholds is inferred from the congruence of contrast gain parameters derived from the pulsed-pedestal data[31] and parameters from single unit primate retina PC recordings.[32] MC mediation of the steady-pedestal thresholds is inferred from the similarity of contrast gain parameters derived from the pedestal-Δ-pedestal data and parameters from single unit primate retina MC recordings. Although contrast gain is established in the retina, postretinal factors can alter sensitivity and may modify contrast gain parameters.[35] The relative sensitivities of thresholds under the pulsed- and steady-pedestal paradigms are determined by the spatial and temporal presentation parameters. The stimulus parameters in the present experiment were chosen so as to obtain a large separation between inferred MC and PC function. Temporal summation data[31] and spatial summation data[36] show that the optimal conditions for having the MC pathway mediate steady-pedestal thresholds and the PC pathway mediate pulsed-pedestal thresholds are briefly presented test stimuli (<50 ms) subtending approximately 1° visual angle.

This methodology has been adopted for use in a variety of clinical studies.[34,37–44] Further, the chromatic contrast discrimination paradigm developed by Smith et al.[45] extends the achromatic contrast discrimination tasks by evaluating chromatic contrast gain in the PC pathway by using the same spatial and adaptation configuration as for the achromatic paradigm. By this method, we evaluated the association between achromatic and chromatic contrast sensitivity and contrast gain in the PC pathway and determine whether optic neuritis influences the association strength.

Methods

Apparatus and Calibration

The stimuli were displayed on a calibrated 17-inch CRT color monitor (NEC, Dallas, TX, controlled by a 10-bit radius video card hosted in a Macintosh G4 computer; Apple Computer, Cupertino, CA). The CRT display was run at a refresh rate of 75 Hz to ensure that artifacts generated by the raster scan would not affect the discrimination threshold.[46] Calibration procedures have been described elsewhere.[45]

Stimuli

A 2 × 2 pedestal array of four 1° squares (pedestal) separated by 0.06° was set within a uniform 9.2° × 8.7° rectangular surround (Fig. 1). For each trial, one square in the pedestal array was randomly chosen as the test square that differed in luminance or chromaticity from other squares during the stimulus presentation (four-alternative forced choice procedure). The pedestal was either pulsed simultaneously with the test square for 26.6 ms during the trial period (pulsed-pedestal condition) or presented continuously (the steady-pedestal condition). The stimulus configuration is therefore identical during the test period in the pulsed and steady paradigms. Figure 1 shows the stimulus configurations for the achromatic pulsed-, achromatic steady-, and chromatic steady-pedestal conditions.

Throughout the experiment, the surround was metameric to the equal-energy–spectrum light [L/(L+M) = 0.665] and [S/(L+M) = 1.0]. The surround luminance was set to 12.0 cd/m^2 (115 effective Td in young normal adults[47]). It is possible that rods are active at this light level; however, rod contributions to the MC or PC pathway are very weak for equal-energy–spectrum light stimuli at retinal illuminances higher than 100 Td.[48,49] For luminance discrimination with the pulsed- and steady-pedestal conditions, there were five pedestal contrasts. The

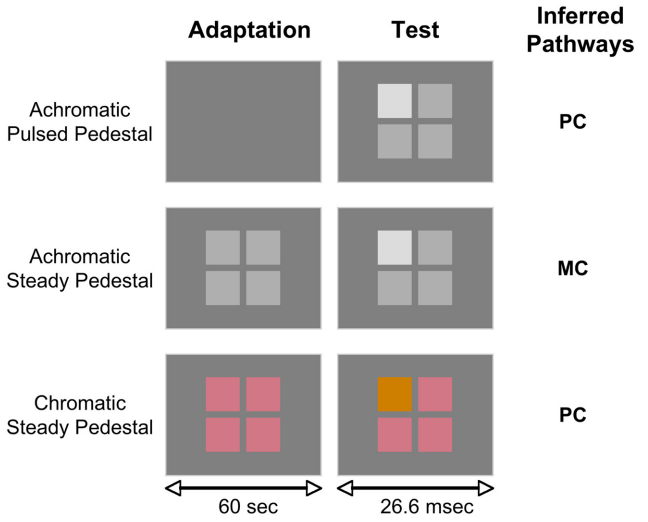

Figure 1. Stimulus paradigms for the achromatic pulsed-pedestal condition (*top*), achromatic steady-pedestal condition (*middle*), and chromatic steady-pedestal condition (*bottom*). All three paradigms shared the same spatial stimulus configuration. A pedestal consisting of a 2 × 2 pedestal array of four 1° squares separated by 0.06° was set within a uniform 9.2° × 8.7° rectangular surround. For each trial, one square in the pedestal array was randomly chosen as the test square, which differed in luminance or chromaticity from other squares during the stimulus presentation. The observer's task was to identify which square differed from the other three. The pedestal was either pulsed simultaneously with the test square for 26.6 ms during the trial period (pulsed-pedestal condition) or presented continuously (the steady-pedestal condition). The achromatic pulsed-pedestal condition reveals PC pathway achromatic contrast gain, the achromatic steady-pedestal condition reveals steady state MC pathway sensitivity, and the chromatic steady-pedestal condition reveals PC pathway chromatic contrast gain.

pedestal luminances were 7.6, 9.5, 12.0, 15.1, and 19.0 cd/m^2. For chromatic discrimination, there were five chromatic contrasts along the L/(L+M) axis with a constant S-cone excitation. The pedestal L/(L+M) chromaticities were 0.62, 0.64, 0.665, 0.68, and 0.70. For color-normal observers, the chromatic steady and pulsed-pedestal paradigms yield similar data.[45] In the present study, we measured L/M discrimination thresholds for the steady-pedestal condition only.

Observers

The sample included 18 control observers (14 women and 4 men) who had no health complaints, best corrected visual acuity of 20/20 or better, and no history of eye disease and 11 observers who had optic neuritis (9 women and 2 men). All provided informed consent in compliance with the Declaration of Helsinki. The normal observer and optic neuritis patients' ages did not differ significantly (mean ± SD: 33.9 ± 9.8 years vs. 38.2 ± 10.7 years; $P = 0.282$). Persons with optic neuritis were recruited from the patient population at the Illinois Eye Institute, Illinois College of Optometry, and the Eye Clinics of The University of Chicago. All observers (other than the investigators) were paid for their services. Patients were selected from a chart review to identify individuals with the following characteristics: acute/subacute loss of vision in one or both eyes occurring over 1 week; improvement in vision beginning at 4 weeks after onset, often associated with loss of color vision and pain on eye movement; were between 18 and 60 years of age with no evidence of systemic diseases associated with optic neuritis or other eye disease. All patients had a comprehensive ophthalmic examination. The episode of optic neuritis had occurred at least 6 months before inclusion and the best corrected visual acuity at the time of entry was better than 20/50. The characteristics of the 11 optic neuritis patients are listed in Table 1. Among the patients, eight had bilateral optic neuritis and three had unilateral optic neuritis. Seven patients had a diagnosis of multiple sclerosis (MS), two (P6 and P9) did not have MS, and in two, the diagnosis of MS was indeterminable (P1 and P10).

Procedure

During experiments, the observer sat in a dimly lit room at 1 m away from the display and monocularly viewed the stimuli. A black eye patch covered the nontested eye. Before each session, the observer was dark adapted for 3 minutes. Each condition began with a 2-minute adaptation period to the surround light level to stabilize the observer's adaptation. For the steady-pedestal paradigm, there was an additional 1-minute period of adaptation to the pedestal and surround. Short auditory beeps signaled the beginning and end of each adaptation period, and the start of each trial. A fixation square (4 min arc), present between trials to aid fixation, was extinguished to signal the trial onset. A random-double staircase procedure was used to determine a discrimination threshold. In one staircase, the test square threshold was measured in an increment direction, in the other, a decrement direction. During each trial, the observer's task was to identify the location of the test square within the four-square pedestal array by moving the mouse cursor into the area where the test square appeared. No feedback was provided. Ten reversals were measured for both the increment and the decrement staircases. The average of the last six reversals was taken as threshold. Including short breaks, the total test time for all three conditions with one eye was approximately 45 minutes. Once one eye was tested, the observer could choose to test the other eye after an extended break or on another day.

Modeling

The luminance and chromatic discrimination data are presented in the results as the change in L-cone luminance (ΔL cd/m^2) as a function of pedestal L-cone luminance. Note that the L-cone luminance is equivalent to 0.665 of the luminance value for luminance discrimination data, which were fitted by a physiological based contrast response model for MC and PC pathways.[31,33] The achromatic contrast response is described by a Michaelis-Menten saturation function[32]:

$$R = R_0 + R_{max}C/(C_{sat} + C) \quad (1)$$

where R_{max} is the maximum response rate, C_{sat} is the half-maximum contrast response, and C is the stimulus Michelson contrast. Contrast gain is defined as R_{max}/C_{sat}, the derivative of equation 1 at 0 contrast ($C = 0$). Therefore, contrast gain expressed in logarithmic units is linearly related to $-\log(C_{sat})$. A contrast discrimination threshold can be obtained when the differential responses to two contrasts (C and a [$C + \Delta C$]) reaches the criterion, δ. Therefore, the pulsed-pedestal luminance discrimination threshold can be derived from equation 1:

$$\log(\Delta L) = K_{p\_a} + \log[(C + C_{sat\_a})^2] - \log[C_{sat\_a} - k(C + C_{sat\_a})] \quad (2)$$

where ΔL is the discrimination threshold (L-cone cd/m^2), K_{p_a} (p denotes pulsed, a denotes achromatic) is the vertical scaling parameter in logarithmic unit that represents PC-mediated absolute threshold (therefore, $-K_{p\_a}$ represents contrast sensitivity), and k represents δ/R_{max}, which is typically small and was set as 0 when fitting the pulsed-pedestal data. There are two free parameters for the achromatic pulsed-pedestal condition (K_{p_a} and C_{sat_a}). Note that the 0 contrast data were not used for pulsed-pedestal model fitting because the pulsed- and steady-pedestal conditions have the same (0 contrast) stimulus, and detection was empirically established to be mediated by the inferred MC pathway. The steady-pedestal luminance discrimination data for a pedestal luminance, L (in L-cone cd/m^2), are described by

$$\log(\Delta L) = K_{s\_a} + \log(L) \quad (3)$$

Table 1. Clinical Characteristics of ON Patients

ON Patient	Sex	Age (y)	OD				OS				MS
			BVA	HVF (MD)	ON	Onset Year	BVA	HVF (MD)	ON	Onset Year	
P1	F	42	20/20	−3.29	Yes	2006	20/20	−4.6	Yes	2006	Unknown
P2	F	29	20/25	−2.43	Yes	2000	20/25	−1.8	Yes	2000	Yes
P3	F	26	20/25	−1.16	Yes	2005	20/20	−0.81	No	—	Yes
P4	F	29	20/20	−2.97	Yes	2005	20/20	−3.65	Yes	2005	Yes
P5	F	30	20/25	−3.52	Yes	1998	20/25	−1.19	Yes	2002	Yes
P6	F	56	20/25	−0.14	Yes	2006	20/25	0.82	Yes	2006	No
P7	M	40	20/50	−3.52	Yes	1993	20/20	−2.24	Yes	2004	Yes
P8	F	34	20/20	0.48	Yes	2007	20/20	−0.54	No	—	Yes
P9	F	32	20/20	−0.1	Yes	2008	20/20	−1.32	Yes	2008	No
P10	F	55	20/20	−1.25	No	—	20/25	−1.87	Yes	2004	Unknown
P11	M	47	20/30	−1.94	Yes	2008	20/20	−2.77	Yes	2008	Yes

where K_{s_a} is the vertical scaling parameter in logarithmic units, which represents absolute threshold in logarithmic units. Therefore, $-K_{s\_a}$ represents MC-mediated absolute sensitivity.

The L/M chromatic discrimination data were fitted with a model of L and M cone spectral processing based on the spectral opponent PC pathway of primates.[20,26,50] Briefly, after a gain control mechanism of L and M cone excitations, the spectral opponent signal is subject to subtractive feedback. The response to a chromatic contrast change from the adapting chromaticity then follows a static saturation function describing retinal ganglion PC cell responses to contrast changes from their adapted steady state level. The details of the chromatic discrimination model are described elsewhere.[45,51] The L/M chromatic discrimination data were fitted with the model:

$$\log(\Delta L) = K_{s\_c} + \log[(\Delta OPP + OPP_A + SAT_c)^2/SAT] - \log[l_{max}/G(L) + m_{max}/G(M)] \quad (4)$$

where K_{s_c} (s denotes steady, c denotes chromatic) represents the vertical scaling factor expressed in logarithmic units (therefore, $-K_{s\_c}$ for contrast sensitivity), OPP_A represents the spectral response to the adapting chromaticity, ΔOPP represents the change in the spectral response with the pedestal chromaticity from the adapting chromaticity, and SAT_c is the PC spectral processing half-saturation term. Note that the saturation term (SAT_c) does not have the same meaning as that for achromatic discrimination (C_{sat_a}). For achromatic discrimination, C_{sat_a} is in the physical contrast domain, whereas SAT_c is in the spectral response domain. There are two free parameters for the L/M chromatic discrimination model (K_{s_c} and SAT_c).

Statistical Analysis

Three of the patients had unilateral defects based on the clinical criteria defined in the Methods section. The unaffected eyes of the patients were excluded from analysis. Each observer's fitted luminance and chromatic model parameters were used for further statistical analysis. First, we examined the distributions of the parameters. Some of the parameters were not normally distributed. Although a nonparametric approach might be appropriate for analysis because there would be no requirement for normality, it has limitations in controlling confounding factors, such as age, or dealing with correlations between the eyes of the observers. We preferred to rely on parametric methods to compare the fitted model parameters between affected and nonaffected eyes, and a log transform proved satisfactory to establish normality. To examine the functional loss of optic neuritis, we used a generalized estimation equation (GEE) modeling approach to account for correlations between the eyes of the same observer.[52] GEE analysis is a modern version of repeated-measures ANOVA with flexibility for fitting outcome variables with various distributions by application of link functions and specifying the variance–covariance structure in repeated measurements by using a sandwich algorithm. We used an identity link function for the fitted parameters that were considered to have normal distributions. The GEE models compared the parameters between affected eyes (coded as 1) and normal eyes (coded as 0). For all the GEE analyses, age was controlled, because aging is an important factor for MC- and PC-mediated detection or discrimination.[37] Since not all the optic neuritis was identified as caused by MS, we conducted additional GEE analysis with MS patients only. GEE models were used to assess the association between two fitted model parameters and whether the strength association differed between normal observers and optic neuritis patients, with one parameter as the outcome. The independent variables included the other parameter, disease group (affected, coded as 1, vs. normal, coded as 0) and their interaction. A significant interaction would indicate the association strength differs between the groups. When the association between achromatic steady and pulsed paradigms was assessed, the parameters from the pulsed paradigm were used as the outcome variables; when the association between the steady chromatic paradigm and the achromatic pulsed paradigm was evaluated, the parameters from the chromatic paradigm were the outcome variables. When the association between the gain parameter and absolute sensitivity parameter was assessed, the gain parameter was the outcome variable.

Results

First, we investigated the functional loss in optic neuritis by comparing the estimated parameters between the normal observers and optic neuritis patients. Then, we evaluated how the estimated parameters related to each other in the normal observers or patients.

Functional Loss in Optic Neuritis

We estimated the 95% confidence intervals (CIs) for the luminance and chromatic discrimination thresholds for each paradigm as a function of pedestal L-cone luminance (cd/m^2) of the normal observers from their model parameters (equations 2–4). The luminance and chromatic discrimination thresholds of each participant with optic neuritis are plotted in reference to the 95% CI of the normal observers (Figs. 2, 3, shaded bands).

Figure 2 shows the individual optic neuritis patient's luminance discrimination for the pulsed-pedestal (open symbols) and steady-pedestal (filled symbols) conditions and the best-fitting models (lines). Thirteen of the 19 optic neuritis eyes had discrimination data falling outside of the 95% CI of the controls. There is evidence of differential sensitivity losses in MC and PC contrast sensitivity and of changes in the slopes of the PC contrast discrimination function in optic neuritis eyes. Figure 3 shows the individual optic neuritis patients' chromatic discrimination data. Ten of 19 optic neuritis eyes had chromatic contrast discrimination functions that differed in either shape or sensitivity compared with the control limits. The differential effect of optic neuritis on PC-mediated achromatic and chromatic contrast discrimination will be considered next.

To directly evaluate the change in contrast sensitivity to achromatic (inferred MC and PC) and chromatic (inferred PC) stimuli and the contrast gain of the PC pathway to achromatic and chromatic stimuli in patients with optic neuritis, we analyzed the parameters from the physiologically based model. It was first determined by inspection of the distributions of the fitted parameters that there were no major deviations from a normal distribution for K_{p_a}, K_{s_a}, and K_{s_c}. The parameters C_{sat_a} and SAT_c were not normally distributed and log transformations, which are directly related to log contrast gain ($-\log[C_{sat\_a}]$ or $-\log[C_{sat\_c}]$ for contrast gains), satisfied normal distribution criteria and were used for GEE analysis. Figure 4 shows the fitted contrast sensitivities ($-K_{s\_a}$, $-K_{p\_a}$, and $-K_{p\_c}$) and contrast gains ($-\log[C_{sat\_a}]$ or $-\log[C_{sat\_c}]$) in normal eyes and affected eyes in optic neuritis patients. The affected eyes had significantly higher K_{s_a} than did the normal eyes (β [SE] = 0.12 [0.04]; P = 0.005), suggesting optic neuritis. The affected eyes also had higher $\log(C_{sat\_a})$ (β [SE] = 0.35 [0.06]; $P < 0.001$) and higher $\log(SAT_c)$ (β [SE] = 0.18 [0.08]; P = 0.015), suggesting that optic neuritis reduced PC-mediated contrast gain for achromatic and chromatic processing. However, K_{p_a} and K_{s_c} were not significantly different between normal eyes and affected eyes (K_{p_a}: β [SE] = −0.03 [0.04]); P = 0.461; K_{s_c}: β [SE] = 0.53 [0.46]; P = 0.255), indicating optic neuritis did not significantly affect PC-mediated detection sensitivity. Additional analysis with the subset of seven patients with MS revealed the same results. That is, the affected eyes in MS patients had reduced MC-mediated absolute sensitivity ($P < 0.001$) and PC-mediated contrast gain estimated from the achromatic pulsed-pedestal paradigm ($P < 0.001$) and chromatic steady-pedestal paradigm (P = 0.049), but did not alter PC-mediated detection sensitivity

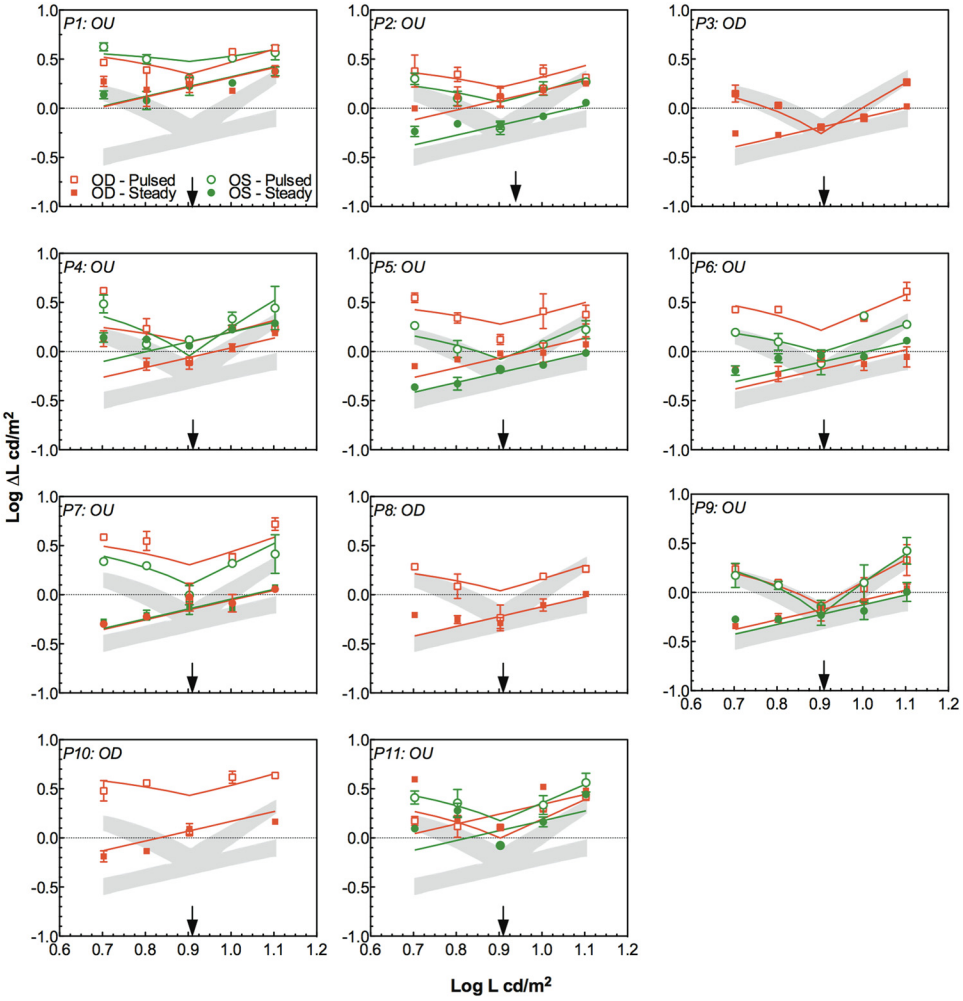

FIGURE 2. The luminance discrimination threshold for optic neuritis patients, in reference to the 95% CI (*shaded area*) defined by the normal observer data. *Open symbols*: data for the achromatic pulsed-pedestal paradigm; *filled symbols*: show data for the achromatic steady-pedestal paradigm; *lines*: model fits of equations 2 and 3. *Arrow*: the retinal illuminance of the surround.

($P = 0.628$ for achromatic pulsed-pedestal paradigm and $P = 0.121$ for chromatic steady-pedestal paradigm).

Association among Fitted Parameters for the PC Pathway

GEE modeling showed that the association strength did not differ between normal observers and optic neuritis patients, as none of the interaction terms between disease and the model parameter that served as the independent variables was significant ($P \geq 0.201$). For the achromatic pulsed-paradigm and the chromatic steady paradigm, both mediated by the PC pathway, the vertical scaling parameters were highly associated (K_{s_c} vs. K_{p_a}: β [SE] = 0.14 [0.04]; $P < 0.001$), indicating a common mechanism determined these values. However, the logarithmic saturation parameters were not significantly associated (log[SAT_c] vs. log[C_{sat_a}]: β [SE] = 0.14 [0.18]; $P = 0.431$), consistent with physiological findings that PC cell responses have higher contrast gain with chromatic stimuli than do achromatic stimuli, and PC chromatic responses may be saturated with a high chromatic contrast.[18] Further, the sensitivity parameter was associated with the logarithmic saturation parameter for the achromatic paradigm (log[C_{sat_a}] vs. K_{p_a}: β [SE] = −0.71 [0.29]; $P = 0.014$). For the chromatic paradigm, the logarithmic saturation and sensitivity parameters were not associated in both observer groups (log[SAT_c] vs. K_{s_c}: β [SE] = −0.79 [1.19]; $P = 0.510$; disease × K_{s_c} interaction: β [SE] = −1.46 [2.00]; $P = 0.465$), suggesting that factors in addition to contrast gain contribute to sensitivity in PC pathway chromatic processing.

DISCUSSION

The comparison between normal observers and optic neuritis patients in achromatic and chromatic discrimination suggests that the eyes affected by optic neuritis had deficits in both the inferred MC and PC pathways, but in different ways. Specifically, optic neuritis reduced MC-mediated absolute sensitivity but reduced PC-mediated contrast gain. Interestingly, the disease did affect the association strength among PC-mediated contrast sensitivities and contrast gains measured from achromatic and chromatic stimuli. Our results imply that, for the MC pathway, the contrast sensitivity loss was larger. However, we could not compare relative loss in contrast gain between the two pathways, since we did not measure MC-mediated contrast gain.

In this study, the contrast discrimination and detection thresholds (Figs. 2, 3) are modeled within a perceptual-decision framework.[31,33,34] That is, a decision ("different or same" for discrimination and "seeing it or not" for detection) will be made once the sensory input reaches a criterion value (i.e., the comparison of sensory input and the criterion). Sensory input is determined by retinal processing, from photoreceptor transduction to ganglion cell contrast responses transmitted via the optic nerve. Perceptual-decision processing is determined in the cortex. In normal observers, the signature V-shape of the contrast discrimination and detection functions (Figs. 2, 3) is defined at a retinal site, principally at the bipolar cell level.[35] Disease alters the contrast gain and sensitivity of the measured contrast discrimination functions by changing neuronal func-

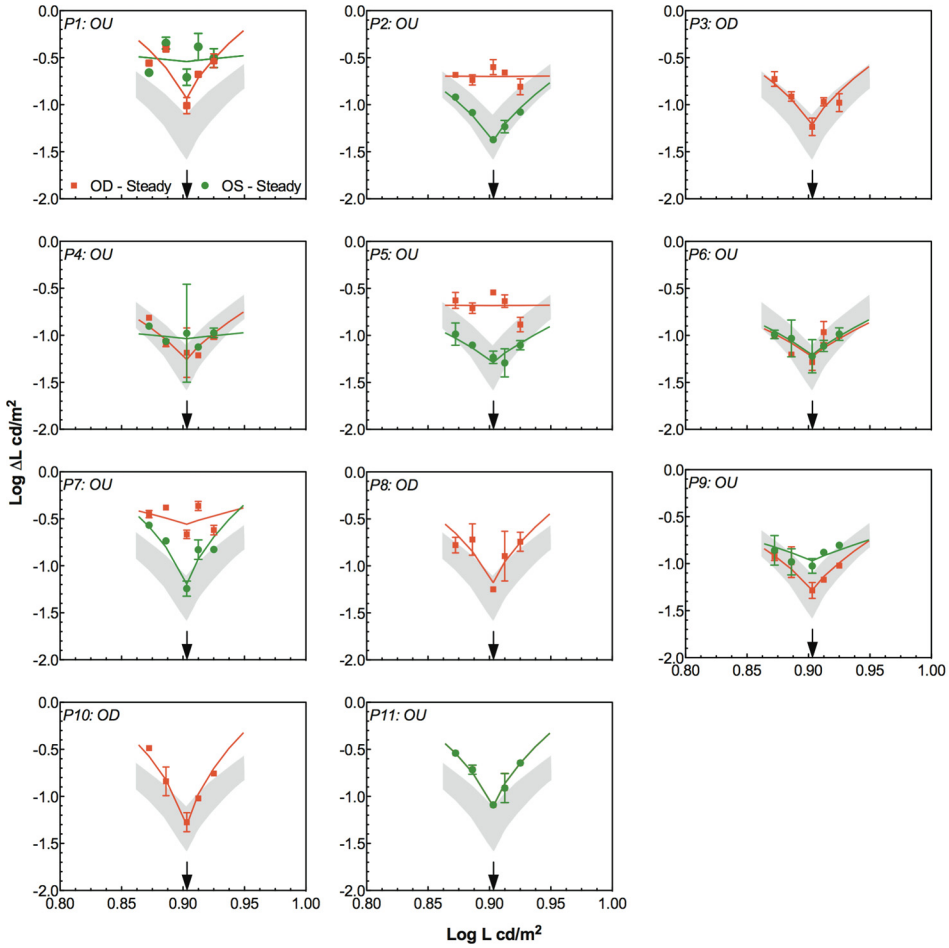

FIGURE 3. The L/M discrimination threshold in optic neuritis patients, in reference to the 95% CIs (*shaded area*) defined by the normal observer data. Lines: model fits of equation 4. *Arrow*: the retinal illuminance of the surround.

tion at one or multiple sites in the visual pathway.[35] Simply, contrast gain and sensitivity can be considered within this framework at three sites: a site before the contrast-processing site (outer retina, photoreceptor level), within the site that defines the signature V-shape (inner retina, bipolar or ganglion cells), or at postretinal sites (optic nerve, cortex).

An alteration in contrast sensitivity in the presence of normal contrast gain can result from a change in quantum efficiency and/or phototransduction noise in the photoreceptors, or a change in decision processing (such as decision criterion variation or a change in sensory information accumulation)[35] in the cortex. At the photoreceptor level, a decrease in quantum efficiency or noise can lead to a change in contrast sensitivity in the pedestal tasks, but even a 10-time decrease (1 log unit) in photopic light level does not reduce cone contrast gain substantially for estimated PC or MC pathways.[53,54] The functional consequences of early changes are complex and not easy to characterize because of the compensatory effects of retinal adaptational mechanisms. Studies show that stimulus noise can decrease chromatic sensitivity without altering contrast gain parameters,[55] and adding noise to the stimuli may differentially impact on PC and MC contrast sensitivity.[56] Therefore, the reduction in MC mediated contrast sensitivity in the optic neuritis patients observed in this study may reflect an anomalous retinal and/or higher order processing. It has been previously recognized that if LGN inputs to the cortex are impaired, there may be adaptive changes in the cortex, such as lateral occipital complexes and other higher visual areas, possibly leading to a change in decision processing.[57–59]

A change in contrast gain alters the slopes of the V-shaped contrast discrimination function and can be caused by an alteration in neural noise (arising in the retinal contrast-processing site; the postretinal site, including optic nerve or cortex) or response compression (from a retinal or postretinal site).[35] Noise arising in the optic nerve or brain can also change the contrast gain. One way of characterizing the precision of information carried in a spike train is by the signal-to-noise ratio. Recordings from cat *X* and *Y*[60] and primate PC and MC ganglion cells[61] show noise to be relatively independent of contrast. Since stimulus related spike rate increases with contrast, the signal-to-noise ratio increases with contrast. If there is sufficient postretinal noise to degrade visual function, the measured contrast gain function will be altered in a specific way. The signal-to-noise ratio for discrimination near the adapting retinal illuminance is lower than the signal-to-noise ratio for discrimination that involves a large step from the adapting retinal illuminance. Thus, the arms of the V will assume shallower slopes. Observers would require more contrast to discriminate contrast changes at low pedestal contrasts compared with higher pedestal contrasts, indicative of a specific type of shallowing of the contrast gain slope. Response compression, however, will produce a different alteration in the contrast gain function. With large contrast steps from the adapting retinal illuminance, a higher than normal contrast is required for discrimination. Thus, discrimination near the adapting retinal illuminance could be normal or near normal, whereas discrimination for a stimulus with a large contrast step from the adapting retinal illuminance could be impaired. We saw V shapes from optic neuritis data that were consistent with either the neural noise interpretation (e.g., P9, OD, Fig. 2) or the response compression interpretation (e.g., P3, OD, Fig. 2). These results suggests that PC-mediated contrast gain loss had

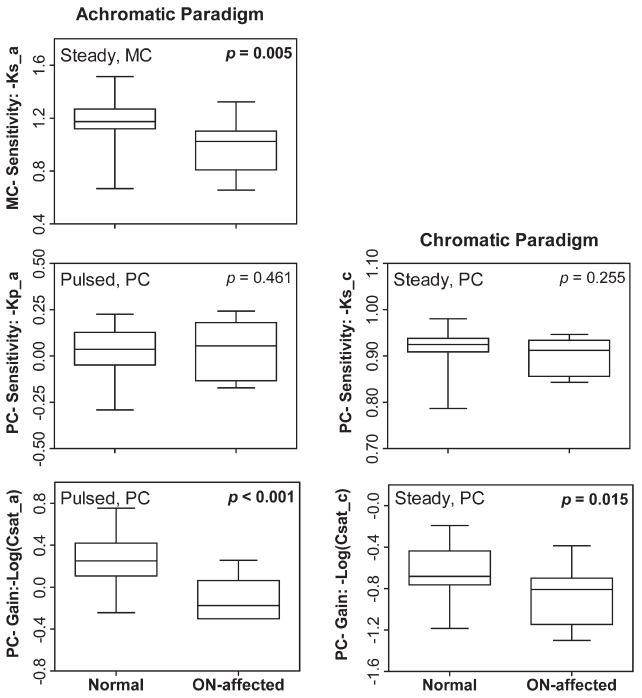

Figure 4. Box plots for the median (50th percentile, the band inside the box) and interquartile range (25th–75th percentile, the bottom and top edges of the box) of the fitted contrast sensitivity and contrast gain parameters in normal eyes and affected eyes. *Left*: model parameters for achromatic paradigms (*top*: steady-pedestal; *middle* and *bottom*: for pulsed-pedestal). *Right*: model parameters for chromatic paradigm. The *P* values are from age-controlled GEE analyses.

multiple etiologies, some of which may be retinal and some postretinal.

As we know from optical coherence tomography (OCT) analysis, retinal nerve fiber layer (RNFL) attenuation can occur in patients with MS who have never had an episode of optic neuritis.[62] That said, those individuals with an established history of optic neuritis typically have significantly more NFL attenuation than do those with MS without optic neuritis.[63,64] The OCT results we have for three patients (5/6 eyes affected) in this study (P2, P9, and P11), showed a reduction in RNFL thickness in five affected eyes (mean ± SD: 74 ± 6.2 μm), compared with normative data. RNFL thicknesses and contrast sensitivity and gain parameters were all negatively correlated, although they did not reach statistical significance because of the small sample size (Pearson correlation between −0.31 and −0.83; $P = 0.08$–0.61). These results imply that alterations in retinal processing play a significant role in reducing MC-mediated sensitivity and PC-mediated contrast gain in patients with optic neuritis, although we cannot rule out the involvement of alterations in higher order processing.

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