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Chromatic discrimination losses in multiple sclerosis patients with and without optic neuritis using the Cambridge Colour Test

ANA LAURA DE ARAÚJO MOURA,[1] ROSANI APARECIDA ANTUNES TEIXEIRA,[1] NESTOR N. OIWA,[1] MARCELO F. COSTA,[1] CLAUDIA FEITOSA-SANTANA,[1] DAGOBERTO CALLEGARO,[2] RUSSELL D. HAMER,[1,3] AND DORA FIX VENTURA[1]

[1]Depto. Psicologia Experimental, Instituto de Psicologia, Universidade de São Paulo, São Paulo, Brasil
[2]Depto. Neurologia, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brasil.
[3]Smith-Kettlewell Eye Research Institute, San Francisco, California

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Abstract

We assessed chromatic discrimination in multiple sclerosis (MS) patients both with (ON) and without (no ON) a history of optic neuritis using the Cambridge color test (CCT). Our goal was to determine the magnitude and chromatic axes of any color vision losses in both patient groups, and to evaluate age-related changes in chromatic discrimination in both patient groups compared to normals. Using the CCT, we measured chromatic discrimination along the protan, deutan and tritan axes in 35 patients with MS (17 ON eyes) and 74 age matched controls. Color thresholds for both patient groups were significantly higher than controls' along the protan and tritan axes ($p < 0.001$). In addition, the ON and no-ON groups differed significantly along all three-color axes ($p < 0.001$). MS patients presented a progressive color discrimination impairment with age (along the deutan and tritan axes) that was almost two times faster than controls, even in the absence of ON. These findings suggest that demyelinating diseases reduce sensitivity to color vision in both red-green and blue-yellow axes, implying impairment in both parvocellular and koniocellular visual pathways. The CCT is a useful tool to help characterize vision losses in MS, and the relationship between these losses and degree of optic nerve involvement.

Keywords: Chromatic discrimination, Multiple sclerosis, Optic neuritis, Cambridge Colour Test

Introduction

Multiple sclerosis (MS) is the most common disabling neurological disease in young adults and the visual pathway is particularly susceptible to damage (Frohman et al., 2005). Visual involvement was first described as early as 1890 by Uhthoff (1890; cited in Volpe, 2001). In MS, a spectrum of pathologies exists, ranging from acute optic neuritis, with relatively sudden loss of vision, to subtle sub-clinical disturbances evident only with neurophysiologic or psychophysical testing (McDonald & Barnes, 1992).

Color vision testing in neuro-ophthalmology is traditionally carried out with Ishihara pseudoisochromatic plates (Ishihara), Farnsworth D-15 test (D-15), Lanthony D-15 desaturated test (D-15d), and the Farnsworth-Munsell 100 hue test (FM-100). All of these tests are effective in detecting congenital color deficiencies, and are useful for monitoring neuro-ophthalmologic dysfunction. Despite its extensive use, the Ishihara was not designed for detecting defects along the blue-yellow axis. Moreover, other hue-arrangement tests are performed using only one saturation and lightness level (Birch, 2001).

Optic neuritis is frequently present in ophthalmological evaluation in patients with MS and can affect one or both eyes. Color vision impairment has been observed in subjects with no history of optic neuritis and tends to be more impaired than luminance sensitivity (Fallowfield & Krauskopf, 1984; Mullen & Plant, 1986; Sartucci et al., 2001; Flanagan & Zele, 2004). A number of investigators have attempted to determine if there is a selective effect on red-green or blue-yellow mechanisms in optic neuritis. Using psychophysical methods, a number of studies found no preference for loss in a specific chromatic channel (Fallowfield & Krauskopf, 1984; Mullen & Plant, 1986; Jackson et al., 2004; Moro et al., 2007). Impairment along both axes has also been shown by electrophysiological evaluation (Porciatti & Sartucci, 1996; Sartucci et al., 2001). Pupil response to a chromatic stimulus has also been used as an additional tool in evaluating this patients' group evaluation. Barbur et al. (2004) found abnormal pupil response in optic neuritis with the color response being more affected than the achromatic

Address correspondence and reprint requests to: Ana Laura de Araújo Moura, Depto. Psicologia Experimental, Instituto de Psicologia, Universidade de São Paulo, Av. Professor Mello Moraes, 1721 Bloco A Sala D-9, 05508-900 São Paulo, SP, Brasil. E-mail: almoura_oft@yahoo.com.br

reflex, and even following the recovery of vision, after a optic neuritis attack, the pupil response remains abnormal (Moro et al., 2007).

However, other data suggest a greater impairment in the red-green pathway (Travis & Thompson, 1989; Flanagan & Zele, 2004; Flanagan & Markulev, 2005). Over the last 10 years, a number of display-based techniques to assess color vision have been developed in order to overcome difficulties in the isolation of the chromatic channels of the human visual system. The use of a chromatic signal masked by spatial or temporal luminance noise can evaluate chromatic discrimination in parvo- and koniocellular pathways (Mollon & Reffin, 1989; Barbur et al., 1994; Smithson & Mollon, 2001). The data obtained with this approach suggests that the processing of color signals is independent of luminance masking noise (Barbur et al., 1994).

The Cambridge Colour Test (CCT, Cambridge Research Systems Ltd, Rochester, UK; Mollon & Reffin, 1989; Regan et al., 1994), evaluate chromatic discrimination in the presence of luminance noise, and has been used in a number of clinical investigations (Regan et al., 1994, 1998; Ventura et al., 2003*a*, 2003*b*, 2003*c*, 2004, 2005*a*, 2005*b*, 2007; Castelo-Branco et al., 2004; Costa et al., 2006, 2007; Silva et al., 2005; Simunovic et al., 1998). The CCT is a computerized test that evaluates color discrimination thresholds along the protan, deutan, and tritan color confusion axes, and which generates discrimination ellipses, thus providing quantitative and qualitative evaluation of color vision performance. A chromatic target (e.g., a Landolt C pattern), is presented within luminance and spatial noise to avoid discrimination based on achromatic cues. The target chromaticity is changed along a given direction in color space, toward the background chromaticity, until a threshold is determined, using a dynamic forced-choice psychophysical staircase. CCT provides two protocols of testing. One of the procedures, the Trivector Test, is carried out simultaneously for the three directions in color space, determining protan, deutan and tritan thresholds. When determining a discrimination ellipse, several vectors around the background chromaticity are tested, two at a time in interleaved staircases. In the second procedure, the thresholds are determined for these directions and the associated color discrimination deficits are compared to control data.

The aim of this study was to assess the chromatic discrimination in MS patients both with and without a history of optic neuritis using the CCT in order to determine the magnitude, progression and chromatic channels of any color vision losses in both patient groups.

Materials and methods

Participants

We tested color vision in 35 patients (nine males) who had been diagnosed with MS, with ages between 18 and 54 years old (mean = 36.84 ± 10.49 years). Seventy-four controls were also tested (39 males; mean = 31.45 ± 13.7 years with a range from 19 to 63 years). The patients were referred to the study by the Section of Neurology, School of Medicine, University of São Paulo, Brazil. The control group was comprised of workers and students from the University of São Paulo. A summary of clinical details of the patients is presented in Table 1.

Complete ophthalmologic and neuro-ophthalmologic examinations were conducted on all the participants. These exams included evaluation of pupillary reflexes and extraocular motility, slit lamp examination of anterior chamber with LOCS III scoring (Lens Opacity Classification System III), measurement of intraocular pressure, and red-free high intensity ophthalmoscopy. Visual acuity was measured at three meters using an ETDRS logMAR chart (tumbling E). Relative afferent pupillary defect was not seen in any of the 73 eyes tested and optic disc pallor was also not apparent.

Prior neurological examination of the patients revealed minimal disability, with expanded disability status scale (EDSS) scores ranging from 0 to 3.0. Fourteen patients (17 eyes) had a history of acute optic neuritis during the course of their illness. MS patients were divided in two groups, patients with (ON), and without (no ON) a documented history of optical neuritis. There was no history of recent demyelination crises in the month before the tests in any of the patients.

Inclusion criteria for both groups were best corrected visual acuity of 0.0 logMAR or better; absence of ophthalmologic pathologies other than ON; absence of posterior subcapsular cataract, and a maximum of grade 1 for cortical opacity (C1), nuclear color (NC1), and nuclear opalescence (NO1), according to the LOCSIII classification system for lens opacity. The mean disease time was 81.3 ± 12.70 months, ranging from 12 to 312 months.

Equipment and procedure

Color discrimination thresholds were measured using the v2.0 CCT (Mollon & Reffin, 1989; Ventura et al., 2003*a*, 2003*b*) run on a Dell computer with the VSG 2/5 visual stimulus generator (Cambridge Research System), and a gamma corrected Sony FD Trinitron color monitor (Model GDM-F500T9). The monitor was calibrated for luminance with the OptiCAL 200-E photometer (Cambridge Research Systems) using the standard calibration routine of the VSG Desktop library (version 8.0). The CRT phosphor limits in CIE 1976 u', v' chromaticity coordinates, were measured with a Minolta CS1000 photometer: red phosphor (R) $u' = 0.416$; $v' = 0.522$; green phosphor (G) $u' = 0.117$; $v' = 0.559$; blue phosphor (B) $u' = 0.159$; $v' = 0.177$.

The visual stimuli consisted of a Landolt "C" target on a background of neutral chromaticity (CIE 1976 coordinates $u' = 0.1977$, $v' = 0.4698$). Both the target and the background were made up of small discrete patches of variable size (5.7–22.8 arcmin diameter) and luminance (six equal steps between 7.0 and 15.0 cd/m^2)

Tests were performed in a dark room with the experimenter's monitor screen off or dimmed. The subject was positioned three meters away from the stimulus monitor, so that the gap in the Landolt C target subtended 1.25° of visual angle. The subjects were tested in both eyes, monocularly, with the starting eye being randomly chosen.

On each trial, the target was presented randomly in one of four orientations (up, down, left, or right), and the observer's (forced-choice) task was to identify the position of the gap.

We used the Trivector test to measure independent thresholds along the protan, deutan, and tritan axes. Thresholds were measured with a psychophysical staircase procedure, which began with a saturated hue for the target stimulus, at the extreme of the CIE 1976 (L$u'v'$) diagram. The distance between the target and background chromaticity along the corresponding vector was decreased for correct responses and increased for incorrect responses. Staircase step size was changed by using an adaptive procedure, a linear staircase optimized for the CCT (proprietary algorithm from Cambridge Research Systems, Ltd.). The CCT software measured the three thresholds simultaneously by interleaving the three staircases randomly. Response reliability was monitored by interspersed presentation of catch-trials with maximum chromatic saturation. A threshold, the average chromaticity, was computed for each staircase after six reversals. The test lasted 3–5 minutes for each eye.

Table 1. *Gender, sex, diagnostic status, duration of the diagnosis and performance on Trivector Test, represented as the threshold values, for the right and left eyes, in three confusion axes. All patients have visual acuity of 0.0 logMAR. Patient No. 17 tested only OS*

Patients					OD			OS		
N.	Gender	Age	Diagnosis	Duration (months)	Protan	Deutan	Tritan	Protan	Deutan	Tritan
1	M	18	no-ON	12	60	90	103	105	77	59
2	F	19	Left ON	24	62	58	98	48	36	64
3	F	19	no-ON	72	64	48	102	124	103	94
4	F	20	no-ON	19	42	33	61	52	65	99
5	F	23	no-ON	24	51	56	76	89	52	58
6	F	23	Left ON	18	56	36	56	95	70	88
7	F	25	no-ON	96	117	59	72	180	191	137
8	F	26	Right ON	120	56	51	85	62	84	71
9	F	31	Left ON	12	49	76	121	113	29	221
10	F	32	Left ON	120	53	79	172	92	86	163
11	F	32	no-ON	96	29	62	65	33	31	67
12	F	33	no-ON	144	114	93	183	108	64	76
13	M	33	Right ON	36	91	85	136	44	49	70
14	F	34	Right ON	30	161	144	141	84	61	100
15	F	35	OU ON	24	245	206	215	241	255	303
16	F	35	no-ON	12	114	79	129	111	93	114
17	M	36	no-ON	36				47	35	65
18	F	36	no-ON	35	63	50	52	74	41	100
19	M	38	Left ON	38	88	69	102	222	214	131
20	M	38	no-ON	37	46	41	26	85	58	107
21	F	39	Left ON	168	61	63	155	63	53	96
22	F	39	no-ON	24	117	59	72	180	191	137
23	F	42	Left ON	156	78	53	49	245	127	173
24	F	42	no-ON	108	66	63	137	62	77	140
25	M	44	no-ON	84	62	95	184	62	67	132
26	F	46	no-ON	60	205	131	205	83	93	146
27	M	46	OU ON	312	219	263	236	137	183	241
28	F	47	no-ON	121	105	104	205	104	76	161
29	M	49	no-ON	120	284	233	304	154	171	227
30	M	49	no-ON	49	123	139	210	80	155	349
31	F	49	no-ON	168	46	50	45	80	55	99
32	F	52	no-ON	48	111	144	170	107	120	186
33	F	52	no-ON	12	70	63	114	53	67	103
34	F	54	OU ON	204	155	134	243	85	36	212
35	F	55	Left ON	240	86	91	126	148	88	49

Analysis

Statistical analyses were performed using Statistica software (StatSoft V6.0, Inc., Tulsa, OK). Statistical assessment of differences among groups was performed using a one-way ANOVA test, a Tukey test for Unequal N. Linear regression was used to evaluate the effects of age and time of disease on chromatic discrimination. Yates corrected Chi-square was used to assess differences in the proportion of color defects.

This study followed the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the Institute of Psychology of the University of São Paulo, No. 1606. Informed consent was obtained from all participants after a full explanation of the nature of the study and the methods used.

Results

We found that color vision is impaired in patients with MS, even those with no history of ON, consistent with data from some previous studies using different methods (Harrison et al., 1987; Porciatti & Sartucci, 1996; Flanagan & Zele, 2004; Moro et al., 2007). Both patient groups had significantly elevated chromatic discrimination thresholds on the CCT test compared to controls (Fig. 1).

For the no-ON group, the protan and tritan axes were affected ($p < 0.001$). Chromatic discrimination losses were found in 18/52 (34.6%) of the no-ON eyes tested: protan, 7/52 (13.5%); deutan, 2/52 (3.8%); and tritan 4/52 (7.7%). For the ON group, discrimination along all three axes was impaired ($p < 0.001$), with losses occurring in 13/17 (76.5%) eyes: protan, 7/17 (41%); deutan, 1/17 (5.9%); and tritan, 1/17 (5.9%). Four out of the 17 eyes (23.5%) had losses in all three axes (see Table 1).

The two patient groups also differed from each other. Color discrimination thresholds for the ON group were significantly higher than for the no-ON group along all three-color axes ($p < 0.001$).

We also evaluated the color discrimination in MS as a function of age. Knoblauch et al. (2001) have shown that color vision sensitivity decreases with age in normals, with the main factors being changes in light scattering characteristics of the eye and spectral absorption (Hennelly et al., 1998). Consistent with Knoblauch's results, our control group had a significant, progressive

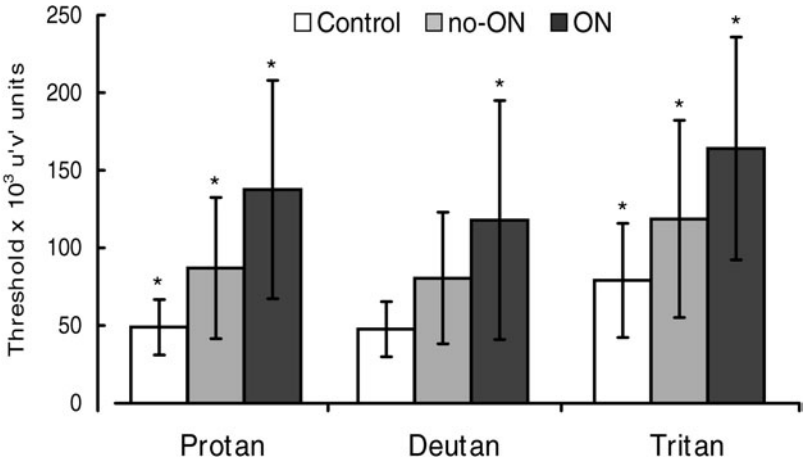

Fig. 1. Average discrimination (± SD) along the three chromatic axes for control eyes (open bars), patients with MS without ON ($n = 56$; gray bars), and patients with a history of ON ($n = 17$; black bars). Except for the deutan axis in the no-ON group, both ON and no-ON eyes display markedly higher thresholds than controls. Stars indicate that there is statistically significant difference ($p < 0.001$) between each patient group and controls. The loss along the deutan axis for the no-ON group was marginally significant ($p = 0.05$).

color discrimination reduction with the age, for all Trivector parameters ($p < 0.001$): protan, 0.56 ± 0.14 $u'v'$/year; deutan, 0.61 ± 0.13 $u'v'$/year; and tritan 1.5 ± 0.30 $u'v'$/year. (○ and solid lines, Fig. 2).

For the ON group, we found a progression of color vision loss with age, but with high variability and thus no statistical difference from controls ($p < 0.15$): protan, 2.14 ± 1.6 $u'v'$/year; deutan, 1.85 ± 1.82 $u'v'$/year; and tritan, 2.47 ± 1.67 $u'v'$/year. (× and dashed lines, Fig. 2).

For the no-ON group, we observed a color discrimination reduction that progressed two times faster than in controls ($p < 0.02$): protan, 1.0 ± 0.6 $u'v'$/year; deutan, 1.4 ± 0.5 $u'v'$/year; and tritan, 3.0 ± 0.7 $u'v'$/year (+ and dot-dashed lines, Fig. 2).

Discussion

The present results show statistically significant losses in chromatic discrimination in MS patients as assessed by the CCT. The impairment is present in MS even with no history of optic neuritis (Harrison et al., 1987; Porciatti & Sartucci, 1996; Flanagan & Zele, 2004), although the ON group had more impairment. Both patient groups manifested significant losses along the protan and tritan axes, and the ON group had losses along the deutan axis as well.

As described in previous studies, patients with MS and ON may present selective loss of visual function with larger impairment in color vision than in achromatic contrast sensitivity (Mullen & Plant, 1986; Sartucci et al., 2001; Barbur et al., 2004). These findings suggest that color vision tests may be more effective for detection of changes in visual function in this group of patients.

In the present results, losses along the deutan axis occurred in the ON group, and both patient groups manifested losses along the protan axis. However, there was a tendency for a higher prevalence of protan losses in the ON group (41% affected eyes in the ON group versus 13.5% in the no-ON group, $p = .061$). The red-green color defects found in both patient groups agree with Kollner's rule, i.e., diseases of the optic nerve affect the red-green channel

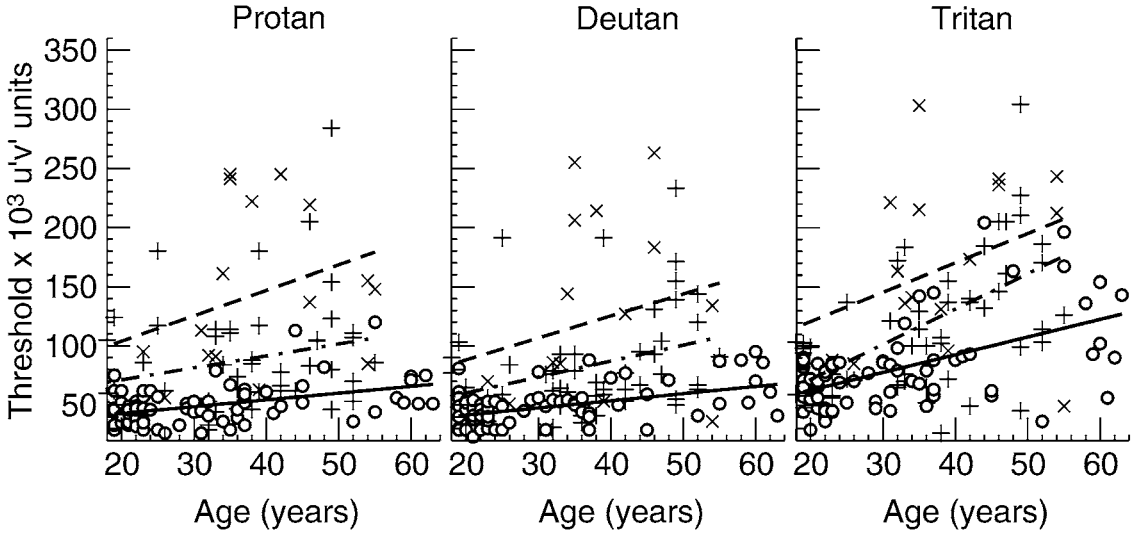

Fig. 2. Age-related changes in chromatic discrimination. Threshold discrimination scores along the protan, deutan and tritan axis versus age in years. In each panel, ○, + and **x** represent the scores for controls, no-ON, and ON, respectively. The solid, dot-dashed and dashed lines represent the least-square linear fits for the control, no-ON, and ON groups, respectively.

(Pokorny & Smith, 1986). Such a tendency would suggest a greater impairment in the parvocellular pathway, consistent with some results with other optic neuropathies such as Leber's hereditary optical neuropathy (Ventura et al., 2007), but not others (e.g., Ventura et al., 2005*a*, 2005*b*; Gualtieri et al., 2008).

The losses in the no-ON group are consistent with a study that found color defects in this group using the Ishihara and FM-100 hue tests (Harrison et al., 1987). Such findings may reflect the presence of a sub-clinical form of optic neuritis in no-ON patients, as recently suggested by Jackson et al. (2004).

A notable finding of this study is that color vision losses progress with age even in MS patients without ON, and this progression is about two times faster than that due to the natural aging process (control data Fig. 2). We do not know whether the losses in MS are due to independent (progressive) neural mechanisms that are simply added to the normal aging losses, or if they reflect some sort of interaction between MS and the natural aging process. This interesting question merits further research.

Although the ON patients also had a progressive reduction in color sensitivity with age, it was not statistically distinguishable from controls. This may be because, shortly following optic neuritis episodes, the contribution of MS *per se* to color vision impairments is approaching its maximum, and the remaining effects are those associated increasing of the age (Fig. 2).

Since MS is a progressive neurodegenerative disease, we also wondered if chromatic discrimination deficits were correlated with the duration of the disease. We defined the disease duration as the number of months since the first clinical identification of demyelination. However, we found no significant correlation for any of the three-color axes, and thus no preference for loss in either the red-green or the blue-yellow chromatic channels, in either patient group. The implication of this null result may be that once demyelination is clinically detectable, the impact on chromatic discrimination reaches a high level.

Clinical assessment of chromatic responses in MS has been performed using electrophysiological methods (Porciatti & Sartucci, 1996; Sartucci et al., 2001) and with different psychophysical approaches than used here (Fallowfield & Krauskopf, 1984; Mullen & Plant, 1986; Flanagan & Markulev, 2005). Both methodologies find impairment in red-green and blue-yellow processing in MS, consistent with our results.

We presented here an efficient alternative color vision test to evaluate losses in chromatic pathways in patients with MS. A number of methods, including measurement of pupil responses, has confirmed such losses. Barbur et al. (2004) and Moro et al. (2007) showed that color sensitivity assessed by pupillary responses is impaired in this group of patients, more than luminance detection. Combining techniques for assessment of color vision pathways should provide a better understanding of the pathophysiology of MS.

Conclusions

The CCT reveals substantial losses in both red-green and blue-yellow discrimination in MS patients. The pattern of the losses suggests that both parvocellular and koniocellular visual pathways are affected, although there is a tendency for a higher prevalence of loss in the red-green (parvocellular-mediated) pathway. Age-related losses in chromatic discrimination in the no-ON group progressed significantly faster than controls. The difference in these rates likely reflects the effects of neural losses due to MS *per se*, combined with losses due to optical/filtering changes with age (Knoblauch et al., 2001; Hennelly et al., 1998). The CCT is a useful tool to help characterize vision losses in MS, and the relationship between these losses and degree of optic nerve involvement. In addition, it may help in early detection and thus aid in effective clinical management of the disease.

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