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Color vision is strongly associated with retinal thinning in multiple sclerosis

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Abstract

Objectives: Multiple Sclerosis (MS) frequently causes injury to the anterior visual pathway (AVP), impairing quality of life due to visual dysfunction. Development of biomarkers in MS is a high priority and both low-contrast visual acuity (LCVA) and time-domain optical coherence tomography (TD-OCT) have been proposed as candidates for this purpose. We sought to assess whether psychophysical assessments of color vision are similarly correlated with structural measures of AVP injury, and therefore augment measures of visual disability in MS.

Methods: We studied the association between high-contrast visual acuity (HCVA), LCVA, color vision (Hardy–Rand–Rittler plates (HRR) and Lanthony D15 tests) and OCT, using both high-resolution spectral-domain OCT (SD-OCT; Spectralis, Heidelberg Engineering, Germany) and TD-OCT (Stratus, Carl Zeiss, US) in a cohort of 213 MS patients (52 with previous optic neuritis) and 47 matched controls in a cross-sectional study.

Results: We found that MS patients have impairments in HCVA and LCVA ($p < 0.001$) but that they suffer from even more profound abnormalities in color discrimination ($p < 0.0001$). We found strong correlation between color vision and SD-OCT measures of retinal nerve fiber layer (RNFL) thickness (average RNFL, $r = 0.594$, $p < 0.001$) and papillomacular bundle thickness ($r = –0.565$, $p < 0.001$). The correlation between OCT scores and functional visual impairments of all types was much stronger for SD-OCT than for TD-OCT.

Conclusion: Our results indicate that color vision is highly correlated with these OCT scores when compared with traditional measures of visual acuity. Also we found that SD-OCT is superior to TD-OCT for detecting anterior visual pathway damage in MS. This makes both color-visual measures and SD-OCT strong candidate biomarkers of disease progression.

Keywords

color vision, imaging, multiple sclerosis, optic nerve, retina, spectral-domain optic coherence tomography (SD-OCT), visual loss

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Introduction

Multiple sclerosis (MS) patients frequently develop injury to the anterior visual pathway including demyelination of the retrobulbar nerve and axonal injury to the nerve and retina.[1,2] This injury leads to a reduced quality of life and causes modest impairment in high-contrast visual acuity (HCVA) and more pronounced deficits in low-contrast vision that have been well characterized.[3] Low-contrast visual acuity (LCVA) is frequently altered in patients with MS and this measurement is more sensitive to subjective visual complaints than high-contrast letter acuity.[4,5] Many patients with MS also report subjective impairment in color discrimination[6–8] especially following acute optic neuritis (ON). However, unlike in congenital color deficits, the physiology and even the phenomenology of color visual impairment in MS is poorly understood.[6,9–10] MS can result in damage to the retina, optic nerve, chiasm and optic tract, as well as the lateral geniculate nucleus (LGN), radiations, primary visual cortex and accessory visual processing

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areas.[2,11] Acquired dyschromatopsia can result from injury anywhere along the visual system, from photoreceptors to the accessory cortex. It is therefore unclear whether color visual impairment in MS is a higher-order 'processing problem' or results from loss of a primary visual stream dedicated to the transfer of critical visual information.

Color vision can be assessed clinically in multiple ways. However, standard bedside assessments in the neurology clinic are rudimentary ('red desaturation') and in the ophthalmology clinic are optimized for the identification and description of congenital color deficits (Ishihara pseudoisochromatic plates). The human eye has been estimated to be capable of distinguishing up to 10 million colors based on the hue (spectral wavelength), saturation ('colorfulness') and lightness (relative brightness) of an object.[12] Colors can be mapped to a visual space based on parameters such as lightness and values on an opponent color scale (both blue–yellow and red–green). Given the complexity of color vision, methods for assessment have been developed for converting color visual performance from simple cap-based organizational tests into a quantitative score.[13,14] These tests theoretically provide a more detailed assessment of color visual impairment than routine clinical evaluations.

The thickness of the retinal nerve fiber layer (RNFL) assessed by optical coherence tomography (OCT) has been proposed as a means of assessing axonal 'integrity' in the anterior visual pathway, and by extension throughout the central nervous system (CNS).[15,16] The thickness of the RNFL is reduced in patients with MS, correlates with brain atrophy and decreases over time [17–20]. OCT scores on traditional time-domain OCT (TD-OCT) are correlated with measures of low-contrast vision.[21] However, limitations in spatial resolution contributed to by the absence of eye tracking and relatively slow speed of image acquisition in classic TD-OCT (e.g. Stratus OCT, Carl Zeiss) have prevented its use in clinical practice to monitor patients with MS. High-resolution, spectral-domain OCT (SD-OCT) provides a significant advance over TD-OCT because its faster image acquisition time overcomes limitations imposed by continuous movement of the eye and permits marked improvements in axial resolution (up to 1–3 μm, compared with 10-μm resolution for TD-OCT)[22] and enhance our capacity to follow patients longitudinally.[23,24] For this reason, SD-OCT provides an opportunity for studying the subtle changes in the retina due to neurological diseases[23,25] and is a promising candidate for becoming a surrogate marker for the development of neuroprotective therapies.[26]

In this cross-sectional study we assessed the presence of anterior visual pathway injury in a cohort of patients with MS with special focus on evaluating bedside color vision tests and its relationship to retinal damage assessed with high-resolution SD-OCT. We also compared the performance between low- and high-resolution SD-OCT.

Methods

Subjects

We studied a prospective cohort of 213 patients with MS (diagnosed according McDonald 2005 revised criteria) and 47 healthy controls followed at the MS center at the University of California, San Francisco. Patients with clinically isolated syndromes fulfilled the criteria of dissemination in time and space. Patients were recruited consecutively at the MS center and were not selected based on clinical symptoms, including vision complaints. MS patients with known ophthalmologic disease (e.g. glaucoma, cataract, malignant myopia) and ON within the prior 6 months were excluded. Prior ON was confirmed by patient history and medical record review. This study received institutional review board approval and written informed consent was obtained from each subject, in accordance with the Declaration of Helsinki. Patients were assessed for their neurological status using the Expanded Disability Status Scale (EDSS). Use of disease-modifying drugs was allowed and recorded. Characteristics of patients are described in Table 1. Disease-free control participants were recruited from among staff and family of patients and had no history of ocular or neurologic disease, including visual acuity (VA) not less than 6/6.

Visual acuity and color vision assessment

Corrected HCVA and LCVA were measured using Early Treatment Diabetic Retinopathy Study letters (ETDRS) on a computerized reading chart (Innova Provideo, Burr Ridge Illinois) in each eye independently. Patients requiring correction wore prescription eyeglasses and evaluations were repeated using a pinhole to help overcome any uncorrected refractive error. Given the requirements for control subjects to have 6/6 vision, it is not possible to determine whether differences in HCVA between MS and controls are due to disease or other factors. ETDRS charts are the standard optotype for HCVA testing in ophthalmology clinical trials. Low-contrast vision was assessed at fixed letter size (6/60) and varying contrast level (similar to Pelli–Robson charts) and with fixed contrast levels and letter size (as is done with Sloan contrast charts including 2.5% and 1.25%) using the same system. Scoring was performed by adding the number of letters identified correctly starting at 6/240 up to 6/3 with 5 letters per level and 20 levels recorded (maximum score = 100) for fixed contrast levels. We performed a validation of this scoring compared with Sloan 2.5% (maximum score 70), which showed high correlation ($r > 0.80$) in a subset of 34 patients between Sloan and the low-contrast measures performed here. Using the fixed letter size approach, scores were recorded as the lowest contrast level in which the subject answered 3/5 letters correctly. Given the extremely high correlation between low-contrast scores at different levels using both fixed

Table 1. Demographics and clinical characteristics.

	Control	MS	*p*-value
n	47	213	–
Sex (male/female)	16/31	93/138	n.s.
Age	37.2 ± 10.2	43.1 ± 14	n.s.
Age at onset	–	34.4 ± 11.1	–
Disease duration	–	9.1 ± 10.8	–
Previous ON	–	52	–
EDSS*	–	2.0 (0–8.5)	–
Disease subtype	–		–
CIS		30	
RR		148	
SP		18	
PP		13	
PR		4	
DMD (yes/no)	–	149/64	–
ETDRS HCVA (logmar scale)**	–0.16 ± 0.262	0.08 ± 0.459	0.001

*Median and range; **Geometric mean (see the Methods section for explanation).
CIS, clinically isolated syndrome; DMD, disease–modifying drug; EDSS, Expanded Disability Status Scale; ETDRS, Early Treatment Diabetic Retinopathy Study letters; HCVA, high–contrast visual acuity; n.s., not siginificant; ON, optic neuritis; PP, primary progressive; PR, progressive relapsing; RR, relapsing–remitting; SP, secondary progressive.

contrast levels and fixed letter size, data reported includes only a single fixed contrast level (2.5%).

Color vision was evaluated using the pseudoisochromatic Hardy–Rand–Rittler (HRR) plates (Richmond Products, US) and the Lanthony D15 desaturated tests (L-D15). L-D15 scores included the color confusion index (CCI), confusion index (CI), and selectivity (or scatter) index (SI).[13,14] HRR was scored based on the number of objects identified correctly in the first 12 plates, including test plates (with a maximum of 20). The CCI is calculated by dividing the calculated distance in color space (CIE 1976/CIELAB) for a specific cap replacement by that distance calculated for perfect replacement. Therefore, higher numbers indicate greater color dysfunction. CI is the ratio between the major radius of the patient's performance and the major radius of a perfect arrangement. People with normal color vision or slightly colorblind persons have a ratio below 1.2. Higher numbers, up to a maximum of 4, indicate more severe color blindness. SI quantifies the amount of polarity (lack of randomness) in cap arrangement. A high score indicates abnormality in a single opponent color system.[13,14] All vision testing was performed under standardized conditions with strictly maintained luminance by a trained technician experienced in vision examinations.

Optic coherence tomography

TD-OCT was performed using the fast RNFL thickness and macular volume protocols on a Stratus OCT machine (Zeiss, Fremont, CA) by a trained technician (AC) masked to the patient's diagnosis as described previously.[27] Scans were repeated three times and assessed for signal strength and centering. Signal strength scores of 7 or less were not used. These results were averaged to obtain both total and quadrant (temporal, superior, inferior and nasal) RNFL thickness in μm.

SD-OCT scans (Figure 1) were performed with the Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany). SD-OCT retinal thickness scans were performed three times by one operator (AC) within one session. SD-OCT correction for spherical errors was readjusted between each measurement. For retinal thickness measurements, 20 × 15° raster scans were performed consisting of 37 high-resolution line scans. A minimum of the *Automatic Real-Time* (ART) of at least 48 was employed for all macular volume scans and ART of at least 16 was employed for all RNFL scans. For peripapillary measurements, a circle scan located at 3.4 cm from the center of the papilla was used. An internal fixation light was used to center the scanning area on the fovea. Scans with insufficient signal to noise (< 24 db) or edge detection/retinal thickness algorithm failure were excluded and measurements were repeated until good quality was achieved. Papillomacular bundle (PMB) thickness is reported as assessed by the standard RNFL quantification algorithm provided by the Spectralis equipment. Briefly, PMB is defined as a 30° arc on peripapillary RNFL scan from 22° to –8° where 0° is defined as the line between the center of the optic disk and foveal depression.

Statistical analysis

Statistical analysis was performed with the SPSS 16 package. Both eyes were included in the analysis. Differences between groups were performed with the *T* or Mann–Whitney test depending on the distribution of variables. Correlations were carried out using the Pearson's bivariate or Spearman rank correlation as appropriate. Multiple linear regressions were used as a multivariate analysis to assess independent association between vision tests and RNFL thickness, adjusted by sex and age. Multivariable regressions were adjusted for gender, race (white versus non-white), age, and history of ON, as well as for inter-eye clustering. We used 2.5% LCVA for the analysis because of floor effects with 1.25% low-contrast vision.[20] Significance was set with $\alpha = 0.05$ (two-tail tests; $p < 0.05$). We applied Bonferroni correction for multiple comparisons for statistical tests assessing predictor variables that are independent of one another (i.e. total RNFL was corrected to account for each independent sector when sector were evaluated independently in the analysis).

Results

Patients with MS have impairments in LCVA compared with healthy controls (Table 2). In addition, we found that they suffer from severe abnormalities in color

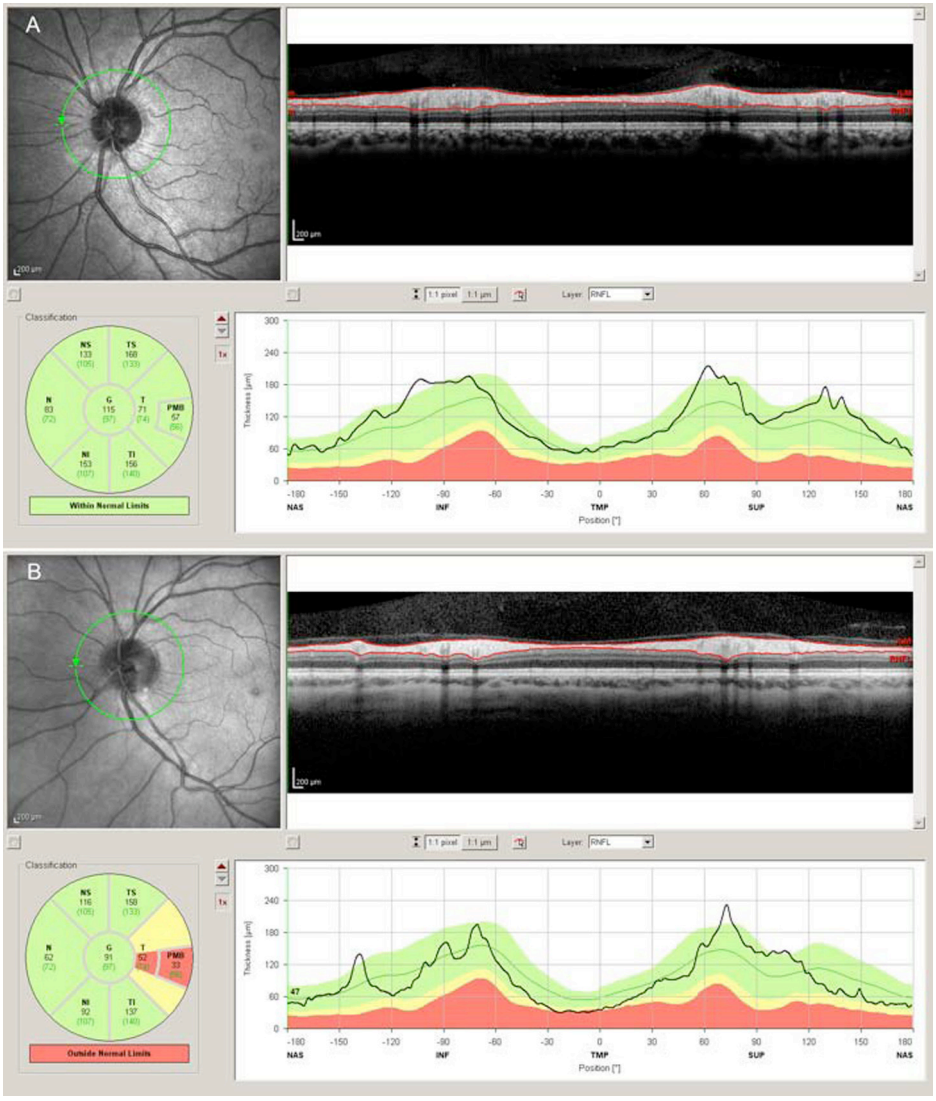

Figure 1. Differences in retinal nerve fiber layer (RNFL) thickness between cases and controls using high-resolution spectral-domain optical coherence tomography (SD-OCT). One representative control (A) and one representative patient with multiple sclerosis (B) are shown. Each case is shown with the fundoscopy image obtained with an infrared camera centered around the papilla level with the circle scan in green (upper-left); the peripapillary SD-OCT, showing the RNFL between the two red lines (upper-right); RNFL thickness, average, by quadrants, and the PMB thickness (bottom-left); and RNFL thickness of the circle scan (black line) with indication of the 95% percentile (green), 5% percentile (yellow) and 1% percentile (red) of the control population (bottom-right). (Color refers to the online version.)

discrimination using both HRR and L-D15 charts. These differences were present in all disease subtypes, and were more severe in patients with progressive disease (Figure 2). Patients have a decreased LCVA and color vision, with a gradient of worsening performance from early MS (CIS) to the progressive forms. Visual outcomes were partially, but not completely, correlated with one another, suggesting they may measure independent features of visual function. For example, some color vision outcomes (HRR and L-D15) were modestly correlated with HCVA and LCVA, but less strongly correlated with one another (data not shown). Weakest correlations were found between low-contrast vision and L-D15, suggesting that they might reflect different aspects of visual function. Further analysis also demonstrated that poor performance on HRR and a high selectivity index (> 2) was associated with a low CCI (< 2) ($p = 0.003$). This suggests that HRR and color confusion index from the L-D15 may reflect different aspects of failure in color discrimination. As expected, visual impairment was more profound in the eyes of patients with previous ON (data not shown). Visual function was weakly correlated with disease duration (ETDRS logmar: $r = 0.21$; $p = 0.001$; LCVA: $r = –0.08$, $p = 0.8$; HRR: $r = –0.18$, $p = 0.001$; L-D15 CCI: $r = 0.17$, $p = 0.006$).

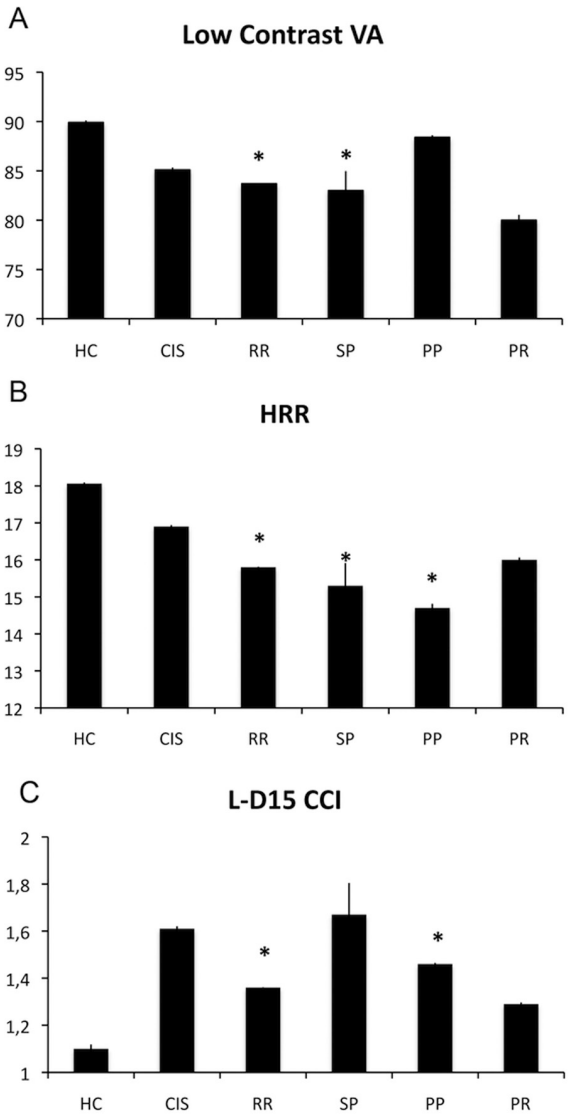

Figure 2. Differences in VA and color vision between disease subtypes.
(A) Low-contrast (2.5%) VA scores; (B) color vision assessed with the HRR; (C) color vision assessed with the L-D15 test and provided as the color confusion index (CCI) score. Results are expressed as the mean + standard deviation. *$p < 0.05$ after correcting for multiple comparisons (Bonferroni correction).
CIS, clinically isolated syndrome; HC, healthy control; Hardy–Rand–Rittler pseudo-isochromatic plates; L-D15, Lanthony 15 desaturated tests; PP, primary progressive; PR, progressive–relapsing; RR, relapsing–remitting; SP, secondary progressive; VA, visual acuity.

After having explored the visual function in patients with MS, we assessed the relationship between function (VA and color vision) and structure (RNFL thickness and macular volume) at the retina level using high-resolution SD-OCT. First, we compared the thickness of the RNFL at the peripapillary region and the macular volume in eyes without previous ON, finding that patients with MS have a decrease in thickness in all regions, being most prominent in the PMB and the temporal quadrant (Table 3). Second, we found correlation between all vision tests and SD-OCT measurements (Table 4), the strongest being between color tests and the RNFL thickness: HRR correlated with the RNFL average ($r = 0.594$, $p < 0.001$) and the L-D15 CCI correlated with the PMB thickness ($r = –0.565$, $p < 0.001$).

We developed linear regression models for predicting HCVA, LCVA and color vision (dependent variables), based on RNFL (global average, PMB and temporal quadrant average) and macular thickness measurements (independent variables) accounting for sex, age, disease duration and history of ON as well as inter-eye correlations in patients. We found that high-contrast vision (logmar) correlated ($r = 0.55$) with macular volume ($p < 0.0001$). Similarly, LCVA correlated ($r = 0.57$) with macular volume ($p < 0.0001$). Color vision (HRR) also showed a strong correlation ($r = 0.65$) with average RNFL thickness ($p = 0.003$), temporal quadrant ($p = 0.019$) and macular volume ($p = 0.009$). Moreover, L-D15 CCI also showed strong correlations with macular volume ($r = 0.58$; $p = 0.002$), PMB RNFL thickness ($r = 0.64$; $p = 0.001$) and temporal quadrant RNFL thickness ($r = 0.61$; $p = 0.002$).

Finally we compared the performance of SD-OCT with TD-OCT for detecting abnormalities in patients with MS. We found that SD-OCT identified more prominent differences in RNFL thickness than TD-OCT, mainly in average RNFL and temporal quadrant RNFL thickness (Table 5). (PMB thickness was not included in the comparison because it is not recorded with the TD-OCT.) In addition, the correlation between OCT scores and functional visual impairments of all types was stronger for SD-OCT than for TD-OCT (for example, correlations were not found between macular volume and L-D15 CCI on TD-OCT but were robust for SD-OCT, $r = 0.54$). HRR and L-D15 also had slightly stronger correlations for most SD-OCT measures than LCVA, but in general associations for both low-contrast and color vision measures were significant (data

Table 2. Visual acuity and color vision in patients with MS.

	Control	MS	*p*-value
2.5% LCVA	89.91 ± 9.400	82.73 ± 19.686	0.017
HRR	18.06 ± 1.541	15.61 ± 4.325	0.001
L-D15 CCI	1.038 ± 0.072	1.490 ± 0.598	0.009
L-D15 CI	1.044 ± 0.078	1.529 ± 0.535	0.017
L-D15 SI	1.467 ± 0.1002	1.852 ± 0.438	0.145

CCI, color confusion index; CI, confusion index; HRR, Hardy–Rand–Rittler pseudo-isochromatic plates; L-D15, Lanthony 15 desaturated test; LCVA, low-contrast visual acuity; SI, selective index.

Table 3. Thickness of the RNFL and macula in patients and controls with high-resolution SD-OCT. RNFL measurements are expressed in μm, macula measurements are expressed in mm^3 and the macular sub-studies in μm^3.

	Control		MS		*p*-value*
	Mean	SD	Mean	SD	
RNFL average	104.28	10.49	90.16	18.07	<0.0005
PMB	58.50	8.66	50.53	12.31	<0.0005
Nasal superior	108.73	22.23	96.47	26.02	0.015
Nasal average	78.75	15.87	70.99	19.63	0.055
Nasal inferior	119.64	33.76	103.59	29.29	0.005
Temporal inferior	149.62	16.64	129.22	31.20	<0.0005
Temporal average	77.65	13.07	63.32	17.17	<0.0005
Temporal superior	143.14	16.99	122.29	27.54	<0.0005
Macular volume	3.14	0.12	3.01	0.20	<0.0009
Fovea	278.69	23.43	270.05	32.98	0.824
Temporal outer macula	331.27	12.97	316.21	30.66	0.009
Superior outer macula	340.90	13.59	326.02	33.49	0.032
Nasal outer macula	349.44	12.57	333.54	32.79	0.018
Inferior outer macula	339.73	12.27	321.22	31.29	0.009
Temporal inner macula	334.81	16.70	321.40	32.98	0.018
Superior inner macula	349.98	16.22	334.86	35.14	0.045
Nasal inner macula	342.48	17.61	330.17	34.31	0.171
Inferior inner macula	346.03	15.39	330.69	32.99	0.018

PMB, papillomacular bundle; RNFL, retinal nerve fiber layer; SD, standard deviation.
*Corrected *p*-value for multiple comparisons using the Bonferroni technique

Table 4. Correlations between visual acuity and RNFL thickness measured with high resolution SD–OCT in patients with MS.

		Logmar	LCVA	HRR	L–D15 CCI	L–D15 CI	L–D15 SI
RNFL average	*r*	–0.436	0.363	0.594	–0.424	–0.379	–0.201
	*p**	<0.0001	<0.0001	<0.0001	0.035	0.062	0.336
PMB	*r*	–0.384	0.404	0.368	–0.565	–0.508	–0.265
	*p**	<0.0001	<0.0001	<0.001	0.001	0.010	0.201
Temporal average	*r*	–0.420	0.382	0.491	–0.473	–0.473	–0.215
	*p**	<0.0001	<0.0001	<0.0001	0.017	0.017	0.303
Macula volume	*r*	–0.45	0.387	0.45	–0.52	–0.54	0.36
	*p**	0.001	0.001	0.001	0.01	0.02	0.27
Fovea volume	*r*	–0.17	0.15	0.139	–0.192	–0.196	0.258
	*p**	0.001	0.03	0.047	0.001	0.001	0.44

CCI, color confusion index; CI, confusion index; HRR, Hardy–Rand–Rittler pseudo–isochromatic plates; L–D15, Lanthony 15 desaturated tests; LCVA, low–contrast visual acuity; PMB, papillomacular bundle; RNFL, retinal nerve fiber layer; SI, selective index.
**p*–values associated with the models correcting for inter–eye correlations.

not shown). Additional multivariable models were assessed using each OCT measures as the outcome and each visual test/measure as the predictors. As each test maintained a significant association with the OCT measures, this confirmed that these tests measure independent features of visual dysfunction (data not shown).

Discussion

In this study we have explored visual dysfunction in MS, finding that color vision is frequently and profoundly impaired in the disease. We also found that these tests are strongly associated with OCT measures at all stages of disease and regardless of a history of ON, strongly suggesting that color vision impairment in MS is a consequence of injury to the anterior visual pathway and not postchiasmatic structures or visual cortical areas. Importantly, we have demonstrated that SD-OCT is superior to TD-OCT as it is more closely correlated with every measure of visual function.

We selected HRR plates and L-D15 for this investigation because they are easy and quick to administer and have

Table 5. Differences in the RNFL thickness in patients with MS measured with low-resolution TD-OCT and high-resolution SD-OCT. For comparative purposes, quadrants from SD-OCT were adjusted to the same topography than TD-OCT.

	TD-OCT					**SD-OCT**				
	Control		Case		*p*-value*	Control		Case		*p*-value*
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
RNFL average	94.68	10.81	88.95	15.22	0.028	104.28	10.49	90.16	18.07	<0.0004
Temporal	**69.14**	**12.27**	**58.39**	**15.37**	**<0.0004**	**77.65**	**13.07**	**63.32**	**17.17**	**<0.0004**
Nasal	73.85	15.59	73.05	18.02	1	78.75	15.87	70.99	19.63	1
Superior	112.47	16.46	107.03	20.11	0.224	180.30	27.13	159.93	33.43	0.292
Inferior	123.20	16.05	117.23	21.47	0.256	194.44	34.81	168.95	35.67	0.08
Macula volume	**6.62**	**0.38**	**6.49**	**0.49**	**0.022**	**3.14**	**0.12**	**3.02**	**0.23**	**<0.0001**

*Corrected *p*-value for multiple comparisons using the Bonferroni technique. *p*-values associated with the models correcting for inter-eye correlations
RNFL, retinal nerve fiber layer; SD-OCT, spectral-domain optical coherence tomography; TD-OCT, time-domain optical coherence tomography.

previously been shown to outperform other standard bedside color-vision tests such as Ishihara pseudoisochromatic plates when evaluating acquired color deficits.[28,29] Desaturated caps simplify the color space by removing the effect of saturation on color perception, and have been shown to be excellent tools for the feasible assessment of acquired color-vision abnormalities in the clinic. Color-vision assessments were more strongly associated with OCT scores than are other tests of visual function. This is in agreement with bedside clinical experience ('red desaturation') and subjective complaints of color impairment.[7,8] Moreover, HRR and L-D15 are only partially collinear, implying that they may test different features of the color system. It has been suggested that HRR more accurately assesses impairment in blue–yellow discrimination and L-D15 is better suited for assessing impairment in red–green discrimination,[28,29] which would comport with our findings. Prior research has failed to demonstrate a standard pattern of color deficiency in MS.[10] Our findings with regards to selectivity index and HRR scores suggest that although MS patients as a whole may not have a uniform pattern of color deficiency, groups of patients may have a particular pattern of color deficit (i.e. red–green > blue–yellow or blue–yellow > red–green). Future work could evaluate whether patterns of visual deficits (low-contrast deficits or particular color deficits) provide a useful means for clinical segregation of patient groups.

Color vision has been described to be particularly susceptible to injury in other retinal degenerative diseases, such as acquired color deficits with exposure to industrial toxins or abnormality in blue–yellow discrimination in glaucoma.[30] Color deficits may reflect a particular pattern of injury in the retina (i.e. greater susceptibility of particular populations of retinal ganglion cells, bipolar cells or photoreceptors). The strongest correlations we detected were between color-vision scores and structural measures of injury to the central retina (macular volume and RNFL thickness in the PMB). This is an indicator of good functional specificity since color vision is mainly served by the macula and further suggests that MS patients are particularly susceptible to injury in these fibers pathways. Although, we cannot rule out the possibility that some of the color abnormalities we observed could be the result of injury to the posterior or accessory visual pathways, the correlations we have seen here suggest that a component of color impairment is secondary to retinal injury.

The introduction of high-resolution SD-OCT is an enormous technological advance because of improved accuracy and spatial resolution (including 3D images combining OCT and confocal imaging), which allow the performance of accurate in vivo imaging of the human retina with the ability to identify the subtle tissue changes that occur over time in neurological diseases.[22] In our study, we found that SD-OCT identifies more frequent and more profound differences between controls and patients both in peripapillary RNFL thickness as well as with macular volume. Furthermore, SD-OCT is more strongly associated with every test of visual functional impairment as another testament to its superiority. In addition, the most sensitive visual test in our study, the color-vision test, most strongly correlated with the SD-OCT measurements that are most abnormal in MS, namely the average RNFL and the PMB thickness, indicating a good correspondence between structure and function at the retinal level. Given variability in the exact boundaries of the PMB, improved methods for detecting the PMB at the individual level would likely result in higher correlations than those observed. In the design of our study we provided every potential advantage to TD-OCT including averaging results and providing rigorous laboratory based standards for OCT quality. Despite this SD-OCT appeared advantageous in every regard. For this reason SD-OCT will probably replace TD-OCT for the evaluation of neurological diseases.

Macular volume was clearly decreased in MS measured with SD-OCT unlike TD-OCT. This result could be explained by the improved spatial resolution of SD-OCT,

which allows investigators to better capture subtle changes in macular atrophy. Our results may explain why previous studies with TD-OCT provided conflicting results regarding the involvement of the macula in MS.[18,31–35] The only measurement from the macula that was not different between patients and controls was the fovea, which is mainly composed by photoreceptors and is characterized by the absence of ganglion cells or RNFL. This suggests that the primary process underlying retinal thinning in MS is loss of ganglion cells.

The current interest in the development of neuroprotective therapies for MS requires sensitive and accurate markers of the degenerative process and its response to therapy. Quantitative tests of color vision and SD-OCT of the retina are good candidates as biomarkers for this purpose. SD-OCT is currently used in the search of neuroprotective therapies for glaucoma and proliferative diabetic retinopathy.[36–40] If SD-OCT were to be validated as a useful biomarker for monitoring the degenerative process in the CNS, this could speed the identification of neuroprotective therapies for MS, improving patient's quality of life in the long term.

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Conflict of interest statement

PV and AG have received consultancy fees from Novartis for conducting a clinical study with OCT in MS.

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