



Color perception impairment following optic neuritis and its association with retinal atrophy

Netta Levin³ · Michael Devereux¹ · Atira Bick³ · Nick Baker¹ · Ari Green^{1,2}

Received: 17 October 2018 / Revised: 21 January 2019 / Accepted: 14 February 2019 / Published online: 20 February 2019
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Abstract

Background Emphasis is often placed on the good recovery of vision following optic neuritis (ON). However, patients continue to perceive difficulties in performing everyday visual tasks and have reduced visual quality of life. This is in addition to documented permanent loss of retinal volume.

Methods Seventy-five subjects following monocular ON (> 3 months prior to assessment), were evaluated by the Rabin cone contrast test (CCT). Red, green and blue cone contrast scores were extracted for the affected and fellow eyes. Retinal nerve fiber layer (RNFL) and macular volume (MV) were assessed using optical coherence tomography.

Results Fifty-seven patients had multiple sclerosis and 17 had clinically isolated syndrome. Median time from ON to evaluation was 47 months. Expanded Disability Status Scale (EDSS) ranged between 0 and 6.5 with average of 2 ± 1.3 . Cone contrast scores for red, green and blue in the affected eyes were significantly lower than in the fellow eyes. RNFL thickness and MV were reduced in the affected compared to the fellow eyes. Positive correlations between CCT and RNFL were found in both eyes, but much stronger in the affected eyes ($r=0.72, 0.74, 0.5$ and $0.53, 0.58, 0.46$ for red green and blue in each eye, respectively). Positive correlations between CCT and MV were found in both eyes, but only modestly stronger in the affected eyes.

Conclusions Impaired chromatic discrimination thresholds quantitatively document persistent functional complaints after ON. There is evidence of dysfunction in both the affected eye and the fellow eye.

Keywords Optic neuritis · Multiple sclerosis · Color perception · Retinal nerve fiber layer · Macular volume · OCT

Background

Optic neuritis (ON) is characterized by visual impairment, including loss of visual acuity accompanied by retrobulbar pain worsened with eye movements. While the pain and acuity deficits typically resolve over several weeks to months, many patients continue to experience visual impairment and

resultant reduction in quality of life [1]. These persistent deficits can affect capacity to work especially with increasing reliance on vision for computer-based work. Ongoing subjective visual complaints are consistent with the known permanent damage to the retina and visual pathways that is seen after ON [2].

Many standard clinical color vision tests for patients with acquired visual dysfunction are either non- or semi-quantitative, or are tremendously time consuming/challenging to administer. In the era predating the availability of retinal imaging for quantitative evaluation of retinal injury, color perception was assessed as a secondary endpoint in a subset of subjects enrolled in the Optic Neuritis Treatment Trial (ONTT) [3]. Using the Farnsworth-Munsell 100-hue color test (FM100), 33% of affected eyes and 23% of the fellow eyes were reported as abnormal 5 years following the acute event [4]. No standard color vision dysfunction was detected. Moreover, the type of defect was not consistent within individual patients as they recover [5, 6]. It has been unclear if

✉ Netta Levin
netta@hadassah.org.il

¹ Division of Neuroinflammation and Glial Biology, Department of Neurology, University of California, San Francisco, CA, USA

² Neuro-ophthalmology Division, Department of Ophthalmology, University of California, San Francisco, CA, USA

³ fMRI Unit, Department of Neurology, Hadassah Hebrew University Medical Center, POB 12,000, 91120 Jerusalem, Israel

this inconsistency was driven by the cognitive and attention demands needed for performing this detailed color evaluation technique [7].

More recently, pseudoisochromatic Hardy, Rand, and Rittler (HRR) plates were used to assess color vision in multiple sclerosis (MS) patients [8–10]. Though color vision was found to be commonly affected, no consistent pattern of dyschromatopsia was detected, a result that could probably be derived from each of the employed methods' limitations (limited dynamic range and lack of accurate scoring criteria).

The Rabin cone contrast test (CCT) uses a randomized series of red, green, and blue letters detectable by a single cone type (long, medium and short, respectively) in decreasing steps of contrast to measure the threshold for letter recognition [11]. Thus, this computerized test is easy and quick to administer and is used by the United State Air Force as a standard test of color vision. It provides both quantitative evaluations of color vision and identification of the type and severity of color vision deficiency. Its sensitivity and specificity were determined by a comparison of its scores to anomaloscope and pseudoisochromatic plate results in ~1500 applicants for pilot training. In agreement with the anomaloscope, the CCT showed 100% sensitivity for detection and categorization of color vision deficiency. CCT specificity for confirming normal color vision was 100% for L and M cone tests and 99.8% for S cones. Furthermore, the CCT was recently evaluated in the elderly (~180 normal phakic and pseudophakic eyes) and reported to be valid up to the seventh decade of life even following a cataract surgery [12].

This study was intended to better assess color perception both qualitatively and quantitatively following an optic neuritis attack, and to document its associated retinal damage. Assessments of visual system injury have become increasingly important outcome measurements in assessment of standard disease-modifying therapies as well as reparative and regenerative treatments [13–15]. Highly sensitive quantitative measures that can easily be utilized in a clinical setting are needed for multi-site clinical trials of new possible therapeutic agents. CCT has advantages over other methods in terms of both standardization and quantification. It could be employed with limited technical training required and given automation and presentation method does not require the highly rigid administration of other color vision tests (i.e., does not require a special light box or very limited lighting conditions).

Methods

Standard protocol approval, registration, and patient consent

The University of California, San Francisco Committee on Human Research approved the experimental procedure.

Written informed consent was obtained from all subjects before study inclusion.

Subjects

Patients that were evaluated at the Multiple Sclerosis Center at the University of California, San Francisco (UCSF) between 2012 and 2016 and had a history of optic neuritis were invited to participate. From this cohort, seventy-five patients, following a first ever, single monocular episode of acute ON that occurred 3 months or more prior to assessment were included in the current study. Evaluation of the patients to define optic neuritis was done by a neuro-ophthalmologist. All patients presented with unilateral visual loss, a relative afferent pupillary defect, and an otherwise normal neuro-ophthalmological examination. Patients suffering from bilateral optic neuritis or hereditary dyschromatopsia were specifically excluded.

Disease duration was defined as the time from the first clinically isolated syndrome (CIS) or first MS symptom. Patients were defined as having either ON-CIS, relapsing remitting MS (RRMS) or secondary progressive MS (SPMS) at the time of their assessment (as defined by Lublin–Reingold criteria) [16]. The Expanded Disability Status Scale (EDSS) [17] was obtained by a certified examiner.

Procedure and data analysis

The affected (AE) and fellow eyes (FE) of each subject were assessed separately for the following measures.

Visual acuity (VA) was measured by Snellen VA chart wearing refractive correction and log-MAR equivalent was calculated.

Spectral domain OCT was performed (SPECTRALIS, Heidelberg Engineering, Heidelberg, Germany), including high-resolution macular scans. The OSCAR-IB quality criteria (based on recognition of obvious problems, poor signal strength, centering of scan, algorithm failure, retinal pathology other than MS related, illumination and beam placement) were met [18]. Segmentation of retinal layers to determine the retinal nerve fiber layer (RNFL) and the macular volume (MV) was performed using automated software algorithm (Heidelberg v1.8.6.0). Data on the pRNFL were obtained using a 12° ring scan placed around the optic nerve head. Data on the macular area were acquired using a macular volume scan (20° × 20° field) centered on the fovea. Laboratory quality control of segmentation was performed to evaluate any algorithm failure before further processing [19].

Color vision was measured by the CCT [11]. In short, the computer-generated CCT presents a randomized series of colored letters visible to a single cone type, red (long), green (medium) and blue (short), in decreasing steps of cone

contrast to determine the threshold for letter recognition. A single letter appears briefly centered in the display and the subject is required to report the letter aloud.

Progressing from most visible down to least visible, the letter appears for a duration of 1.0–1.6 s (duration increases as contrast decreases), followed by an inter-trial interval (gray field) of equal duration. During this time, the subject is required to read the letter aloud, answers are recorded by a technician, and the program then advances to the next trial. The log contrast sensitivity scores are normalized to an intuitive 100-point scale such that each letter that is read correctly counts as five points, making the maximum score 100 and the minimum score 0. The CCT duration is 3 min per eye.

Statistics

Mean values of the different contrast sensitivity scores, RNFL thickness and total macular volume were compared between the affected and the fellow eyes through two-tailed paired *t* test.

Pearson's correlation and linear regression analysis were used to examine relationships between time from acute event, EDSS, retinal measurements and contrast sensitivity scores. Subjects with missing information were removed from this stage of analysis. For all regression analyses, assumption of normality of residual was validated using the Kolmogorov–Smirnov Test.

Results

Demographic and retinal measurements

Seventy-five patients (81.3% women) aged 12–71 years [40.3 ± 12.3 mean \pm SD; only two patients were below 18 (12 and 15)] were included in the study. Fifty-seven had MS (1 SPMS, all others RRMS), 17 had CIS-ON, and 1 did not finish his work-up at the time of evaluation. Half of the patients ($n = 38$) suffered from right ON and the other from left ON.

Time from episode to evaluation ranged between 3 and 685 months with average of 83 ± 115 months (mean \pm SD) and median of 47 months. It should be noted that five patients experienced their attack more than 200 months prior to evaluation; therefore given their outlier status sensitivity, the analysis was performed including these individuals in the analysis as well as excluding them to ensure that late progressive injury was not driving our observations.

EDSS ranged between 0 and 6.5 with average of 2 ± 1.3 (mean \pm SD) and median of 2.

Visual acuity was 20/30 or below only in five affected and three fellow eyes. Yet, averaged log-MAR visual acuity

was slightly but significantly higher in the affected (-0.029) versus the fellow eyes (-0.081) ($p = 0.02$).

RNFL thickness and MV were reduced in the affected compared to the fellow eyes ($78.6 \mu\text{m} \pm 16.5 \mu\text{m}$ and $2.9 \text{ mm}^3 \pm 0.14 \text{ mm}^3$ versus $91.2 \mu\text{m} \pm 15.1 \mu\text{m}$ and $3.0 \text{ mm}^3 \pm 0.17 \text{ mm}^3$; $p = 3.6\text{E}^{-09}$ and $p = 1.8\text{E}^{-9}$ correspondingly).

Cone contrast performance was impaired in the affected eyes (Fig. 1)

The mean red, green and blue contrast scores in the affected eyes were lower than in the fellow eyes (72.7 ± 32 , 68 ± 36.1 , and 69.1 ± 36.7 versus 88.8 ± 15.6 , 86.2 ± 20.6 , and 89.8 ± 17.3 for red, green and blue, means \pm SD in the affected and in the fellow eye; correspondingly, $p = 3.2\text{E}^{-06}$; 8E^{-07} ; 2.2E^{-07}).

Strong correlations were found between the three color contrast scores ($r > 0.9$; Fig. 1b).

To help explore whether demographic and structural measures were associated with CCT performance, the independence of these color vision metrics, and the contribution of other factors to color vision performance, a number of models were constructed and evaluated as detailed below and in the following sections.

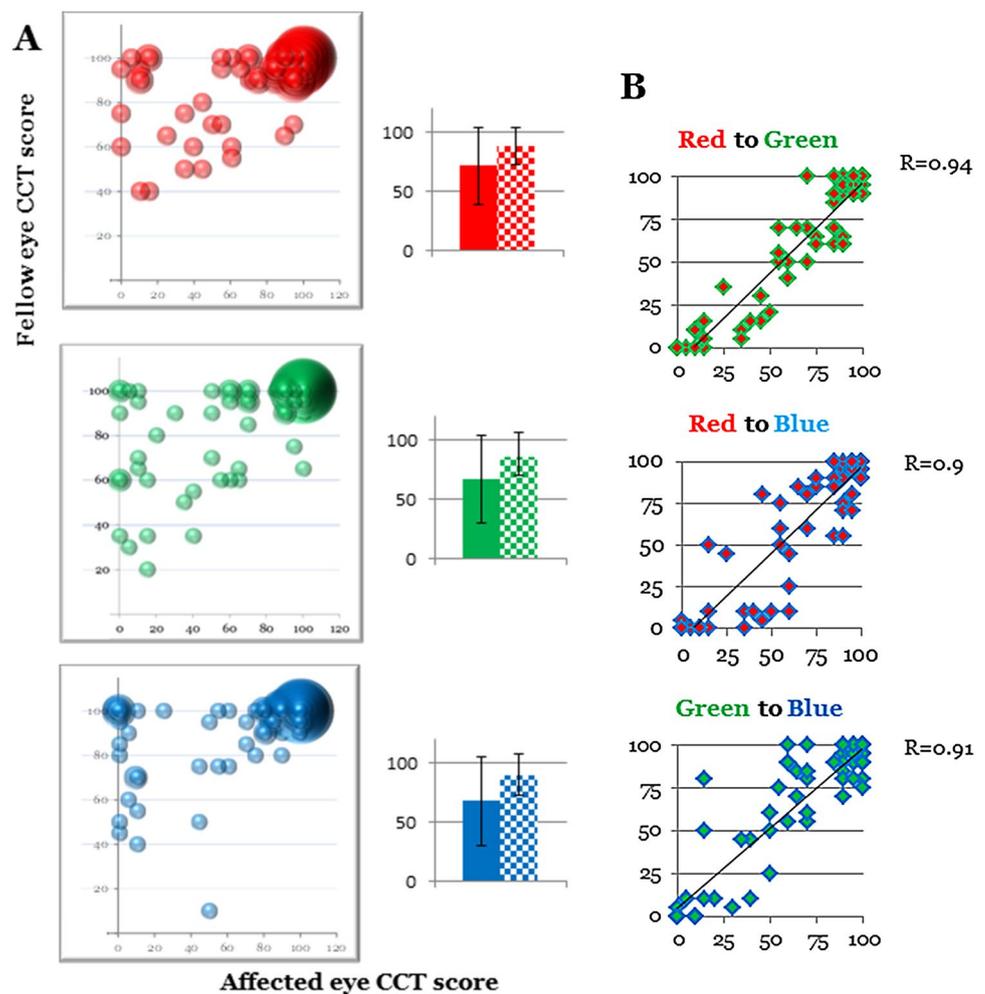
A regression model, which included demographic factors (i.e., gender, age, history of MS, right or left eye involvement, EDSS and time from acute event) significantly predicted mean AE color perceptual abilities ($F_{(6,66)} = 7.4$, $p = 4.4\text{E}^{-06}$). Factors that contributed significantly to the model were gender ($t = 2.1$, $p < 0.05$; females showed better color perceptual abilities), history of MS ($t = 2.5$, $p < 0.05$; patients with previous MS showed better color perceptual abilities) and time from acute event ($t = -2.96$, $p < 0.005$; patients with longer time from acute event showed worse color perceptual abilities). Similar results were found for each color independently as well.

Color contrast sensitivity abilities correlate with retinal thickness, in the affected but also in the fellow eyes (Fig. 2)

In the affected eyes, strong positive correlations were found between each color score and the RNFL. The Pearson correlation for the red CCT was $r = 0.72$, $p = 7.4\text{E}^{-13}$; for the green CCT was, $r = 0.74$, $p = 6.9\text{E}^{-14}$; and for the blue CCT was $r = 0.75$ $p = 1.1\text{E}^{-14}$.

In the fellow eyes, we found a similar pattern: positive correlations were found between each color score and RNFL thickness. Nevertheless, the strength of these correlations was less pronounced. In the fellow eye, for the red CCT, $r = 0.53$, $p = 1.2\text{E}^{-06}$; the green CCT was $r = 0.58$, $p = 8.4\text{E}^{-08}$; and the blue CCT was $r = 0.46$, $p = 4.2\text{E}^{-05}$.

Fig. 1 a CCT scores from the affected eyes are plotted against corresponding scores from the fellow eyes for the red (upper graph) green (middle graph) and blue (lower graph) scores. Right bar graphs stand for corresponding averaged scores. Solid fill for affected and checkerboard fill for the fellow eyes. Error bars represent standard deviations. **b** Affected eyes' red scores are plotted against green scores (upper graph), red scores are plotted against blue scores (middle graph) and green scores are plotted against blue scores (lower graph)



Furthermore, supporting the findings from RNFL, significant correlations were also found between each color score and MV. Here the correlations were only modestly stronger in the affected eye when compared to the fellow eye. For the affected eyes, the red CCT score, $r=0.57$, $p=2E^{-7}$; green CCT score, $r=0.63$, $p=3.2E^{-9}$; and blue CCT score $r=0.6$, $p=1.9E^{-8}$. For the fellow eyes, the red CCT score, $r=0.52$, $p=3E^{-6}$; green score, $r=0.56$, $p=2.4E^{-7}$; and blue score $r=0.44$, $p=9.4E^{-5}$.

Adding the RNFL thickness and MV (of both eyes) to the previous demographically based regression models significantly contributed to the predicted color perceptual abilities in each eye: $F(10, 59)=20.07$, $p=1.66E^{-15}$, for the affected; and $F(10, 59)=6.98$, $p=4.22E^{-07}$, for the fellow eye.

Factors that significantly contributed to the prediction of color vision scores in the affected eye included gender ($t=3.44$, $p<0.005$; females showed better color perceptual abilities), the existence of MS ($t=2.74$, $p<0.01$; patients with previous MS showed better color perceptual abilities), age at visit ($t=-2.11$, $p<0.05$; the older the patient is the worse the color perceptual abilities are) and

time from acute attack ($t=-2.93$, $p<0.005$; the longer the time from the attack is the worse the color perceptual abilities are). However, the strongest association was for RNFL thickness in the affected eye ($t=3.53$, $p<0.001$; the thicker the RNFL is the better the color perceptual abilities are).

In the fellow eye, only age at visit ($t=-2.00$, $p<0.05$; the older the patient is the worse the color perceptual abilities are) and MV contributed to the prediction of color vision scores ($t=2.86$, $p<0.006$; the larger the MV is the better the color perceptual abilities are).

To better understand the relative contributions of RNFL thickness and MV on CCT color perceptual performance in each eye individually, a model was constructed with only these two variables as predictors. For the affected eye, all predictive values came from the RNFL thickness ($p<9.07E^{-08}$, $F(2, 67)=51.66$, $p=2.67E^{-14}$, $t=5.99$), while the MV contribution was not significant ($p=0.1$). For the fellow eye, both factors significantly contributed to the model ($F(2, 67)=31.722$, $p=2.03E^{-10}$, RNFL thickness $p=0.0004$, $t=3.71$; MV $p=0.001$, $t=3.43$).

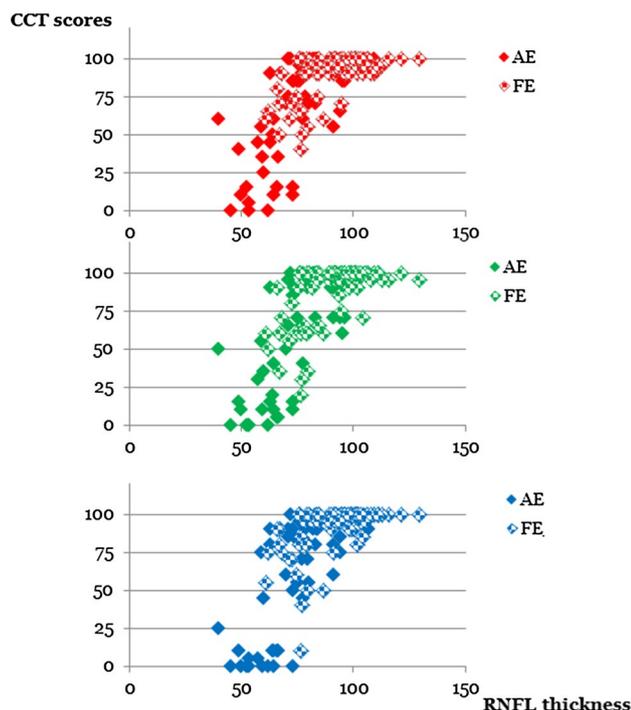


Fig. 2 CCT scores are plotted against corresponding RNFL thickness measurements for the red (upper graph) green (middle graph) and blue (lower graph) scores. Solid fill markers for the affected and checkerboard fill markers for the fellow eyes

Cone contrast performance as a function of time from acute event (Fig. 3)

In the affected eyes, inverse correlations were found between each color score and the time from the acute ON episode. For the red CCT score, $r = -0.5$, $p = 5.5E^{-6}$; for the green CCT score, $r = -0.47$, $p = 2.3E^{-5}$; and for the blue CCT score $r = -0.47$, $p = 1.5E^{-5}$.

In the fellow eyes, inverse correlations were also found. However, the strength of these correlations was much lower. For the red score, $r = -0.36$, $p = 0.001$; for the green score, $r = -0.37$, $p = 0.0008$; and for the blue score $r = -0.36$, $p = 0.001$.

However, these correlations appeared to be driven by the extreme cases, i.e., those who experienced their attack more than 200 months prior to evaluation ($n = 5$). Without those patients, no significant correlations were found between color contrast and time from event. Furthermore, sensitivity analyses repeating the primary analyses detailed above regarding the correlation between cone contrast vision and OCT measures and other demographic factors revealed that inclusion and exclusion of these subjects did not significantly change our results (not shown).

A regression model which included all the averaged color scores could not predict the time from the event either.

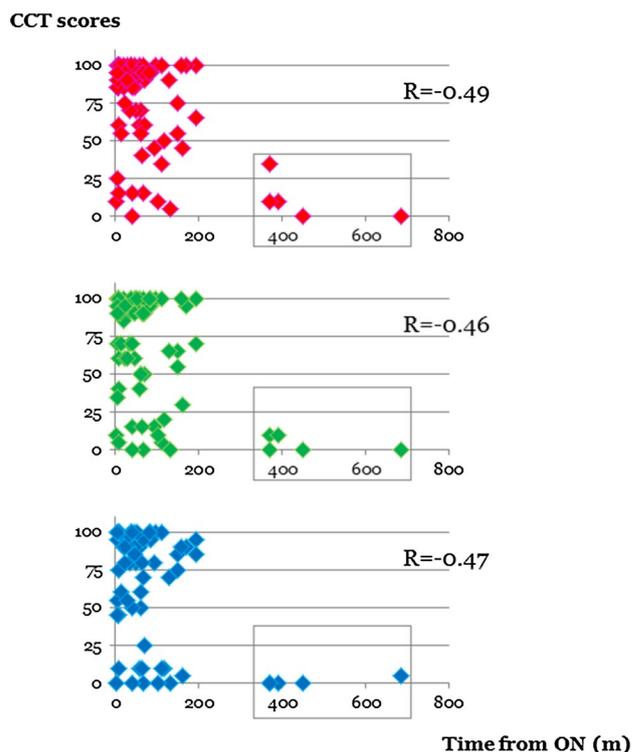


Fig. 3 Affected eyes' CCT scores are plotted against corresponding time from acute event, measured in months, for the red (upper graph) green (middle graph) and blue (lower graph) scores. Gray inset circles five patients who experienced their attack more than 200 months prior to evaluation

Cone contrast performance correlates with disability as reflected in the EDSS

Modest inverse correlations were found between the EDSS scores and the different color contrast sensitivity scores: For the affected eye: red score, $r = -0.28$, $p = 0.01$; green score, $r = -0.36$, $p = 0.001$; and blue score $r = -0.38$, $p = 0.0007$ and for the fellow eye: red score, $r = -0.38$, $p = 0.0008$; green score, $r = -0.33$, $p = 0.003$; and blue score $r = -0.39$, $p = 0.0005$.

Discussion

Though color perception is known to be impaired both during and after optic neuritis, a simple straightforward, quantitative method for assessing this impairment has been lacking, thus limiting the capacity to use color vision assessments as an outcome in clinical trials. The current study provides conclusive evidence that patients exhibit persistent deficits in color perception using a highly quantitative and easy-to-administer color vision test that could easily be employed broadly. Furthermore, this study provides further

evidence (in addition to work already done in low contrast [20] and motion perception [21] that persistent functional impairment can be found in patients after ON—an observation that aligns with patients' clinical complaints.

Consistent with previous reports [5, 6, 8–10], no specific color impairment was found across the cohort, suggesting that color vision impairment in this population is variable and perhaps stochastic. Furthermore, the color deficits detected seem to relate to permanent structural changes in the anterior visual pathway. Significant correlations were evident between each color score and retinal thickness. Interestingly, RNFL explained color vision performance better than any other structural measurements in eyes after ON. Cone contrast performance was not dependent on the time from acute event except for the extreme cases in which the acute event happened decades ago suggesting that a significant proportion of the functional deficit is established early. Color perception was modestly associated with EDSS and may reflect disability not captured by this well-utilized but flawed measure.

Color processing begins at a very early level in the visual system. Trichromacy arises at the level of the receptors with cone populations tuned to colors of different wavelengths for their optimal response. Opponent color processing arises in the inner nuclear layer via horizontal and bipolar cells and continues at the level of retinal ganglion cells. From there, color information is sent to the brain via the optic nerves through the chiasm and tracts to synapse at spatially separated layers of the lateral geniculate nucleus (parvocellular layers of LGN). Color information, as well as other static elements of visual perception, is carried through the parvocellular fibers that are located in the central region of the optic nerve.

Diseases of the optic nerve have been proven to affect color vision in the presence of good visual acuity more profoundly than other eye diseases (macular disease, media opacity, or amblyopia) [22]. Additionally, an increased vulnerability of the parvocellular, compared with the magnocellular, system has been documented [23, 24]. This relatively selective injury has been suggested to be related to the parvocellular fibers' smaller diameter, which may make them either more susceptible to demyelinating injury or less capable of repair. Histopathological evaluation of the visual pathway in MS has revealed rarefaction of ganglion cells in the macular region, again suggesting involvement of smaller axons [25]. Consistent with the hypothesis of high vulnerability of small axons, it is not surprising that a parvocellular-specific modality like color perception represents a useful tool for the diagnosis and follow-up for axonal loss in MS with the added advantage of its functional relevance. Since the impairment is related to failure of conduction of retinally derived action potentials, there is no substantial difference between all

wavelengths and they are similarly affected. The strong correlation between each color score and the thickness of the retinal fiber layer should highlight the functional relevance of the fibers' atrophy.

Thinning of the RNFL following ON is a well-known phenomenon that has been considered to reflect retrograde degeneration (dying back) of the optic nerve [26] and is found to be correlated with visual acuity, low-contrast letter acuity, visual field as well as previous assessment of color vision (for review [2]).

Furthermore, retinal thinning was also reported in CIS patients' eyes that were not clinically affected by ON. Particularly, significant thinning of the ganglion cell layer (GCL) was reported, indicating that retinal neuronal damage can accompany MS independent of a prior history of ON [27]. Two theories were suggested to explain this phenomenon. The first is related to the dying back theory, which can take place both after ON but also following general brain inflammation without specific involvement of the optic nerve [26]. The second suggests that retinal pathology can occur independently of optic nerve pathology. This theory is based on findings in patients exhibiting substantial reduction of MV despite normal RNFL values [28].

Our findings of the notable correlations between color scores and the retinal thickness emphasize again, from a different viewpoint the clinical relevance of retinal thickness. Furthermore, the differential influence of the different layers in the affected compared to the fellow eye may indicate different pathological mechanisms in the two eyes. While retrograde axonal atrophy can explain color perception impairment in the affected eye, a primary neuronal damage may explain this impairment in the fellow eye.

Similar results were reported recently by Lampert et al. [8]. Using HRR, GCL thickness was found to be associated with dyschromatopsia in MS patients' non-ON eyes.

This study is limited by the variability in the age range of the patients, in the time lapse from the acute episode and in the different disease courses and due to the lack of information regarding patients' disease-modifying treatment history. However despite this heterogeneity, previous optic neuritis episodes still leave their mark in the patient's visual system.

As has been previously suggested, the unique accessibility and structure–function correlations provided by the afferent visual system in MS, make vision a useful single functional system to test new MS therapies [29]. This study provides compelling evidence that the CCT is a sensitive visual function test and provides a potentially valuable summary assessment of acquired color vision deficiency in ON and may help us understand the relationship between functional impairment and structural injury in MS.

Acknowledgements Netta Levin and Ari Green thank the Feldman foundation for their support for Professor Levin's sabbatical at UCSF.

Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

- Galetta SL et al (2015) Acute optic neuritis: unmet clinical needs and model for new therapies. *Neurol Neuroimmunol Neuroinflamm* 2(4):e135
- Hanson JV et al (2016) Optical coherence tomography in multiple sclerosis. *Semin Neurol* 36(2):177–184
- Beck RW et al (1992) A randomized, controlled trial of corticosteroids in the treatment of acute optic neuritis. The Optic Neuritis Study Group. *N Engl J Med* 326(9):581–588
- No authors listed (1997) Visual function 5 years after optic neuritis: experience of the optic neuritis treatment trial. The Optic Neuritis Study Group. *Arch Ophthalmol* 115(12):1545–1552. <https://jamanetwork.com/journals/jamaophthalmology/fullarticle/642401>
- Katz B (1995) The dyschromatopsia of optic neuritis: a descriptive analysis of data from the optic neuritis treatment trial. *Trans Am Ophthalmol Soc* 93:685–708
- Schneck ME, Haegerstrom-Portnoy G (1997) Color vision defect type and spatial vision in the optic neuritis treatment trial. *Invest Ophthalmol Vis Sci* 38(11):2278–2289
- Cranwell MB et al (2015) Performance on the Farnsworth-Munsell 100-Hue test is significantly related to nonverbal IQ. *Invest Ophthalmol Vis Sci* 56(5):3171–3178
- Lampert EJ et al (2015) Color vision impairment in multiple sclerosis points to retinal ganglion cell damage. *J Neurol* 262(11):2491–2497
- Martinez-Lapiscina EH et al (2014) Colour vision impairment is associated with disease severity in multiple sclerosis. *Mult Scler* 20(9):1207–1216
- Villoslada P et al (2012) Color vision is strongly associated with retinal thinning in multiple sclerosis. *Mult Scler* 18(7):991–999
- Rabin J, Gooch J, Ivan D (2011) Rapid quantification of color vision: the cone contrast test. *Invest Ophthalmol Vis Sci* 52(2):816–820
- Fujikawa M et al (2018) Evaluation of clinical validity of the Rabin cone contrast test in normal phakic or pseudophakic eyes and severely dichromatic eyes. *Acta Ophthalmol* 96(2):e164–e167
- Balcer LJ et al (2007) Natalizumab reduces visual loss in patients with relapsing multiple sclerosis. *Neurology* 68(16):1299–1304
- Raftopoulos R et al (2016) Phenytoin for neuroprotection in patients with acute optic neuritis: a randomised, placebo-controlled, phase 2 trial. *Lancet Neurol* 15(3):259–269
- Green AJ et al (2017) Clemastine fumarate as a remyelinating therapy for multiple sclerosis (ReBUILD): a randomised, controlled, double-blind, crossover trial. *Lancet* 390(10111):2481–2489
- Lublin FD, Reingold SC (1996) Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical trials of new agents in multiple sclerosis. *Neurology* 46(4):907–911
- Kurtzke JF (1983) Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 33(11):1444–1452
- Schippeling S et al (2015) Quality control for retinal OCT in multiple sclerosis: validation of the OSCAR-IB criteria. *Mult Scler* 21(2):163–170
- Cruz-Herranz A et al (2016) The APOSTEL recommendations for reporting quantitative optical coherence tomography studies. *Neurology* 86(24):2303–2309
- Mowry EM et al (2009) Vision related quality of life in multiple sclerosis: correlation with new measures of low and high contrast letter acuity. *J Neurol Neurosurg Psychiatry* 80(7):767–772
- Raz N et al (2011) Sustained motion perception deficit following optic neuritis: behavioral and cortical evidence. *Neurology* 76(24):2103–2111
- Almog Y, Nemet A (2010) The correlation between visual acuity and color vision as an indicator of the cause of visual loss. *Am J Ophthalmol* 149(6):1000–1004
- Porciatti V, Sartucci F (1996) Retinal and cortical evoked responses to chromatic contrast stimuli. Specific losses in both eyes of patients with multiple sclerosis and unilateral optic neuritis. *Brain* 119(Pt 3):723–740
- Evangelou N et al (2001) Size-selective neuronal changes in the anterior optic pathways suggest a differential susceptibility to injury in multiple sclerosis. *Brain* 124(Pt 9):1813–1820
- Toussaint D et al (1983) Clinicopathological study of the visual pathways, eyes, and cerebral hemispheres in 32 cases of disseminated sclerosis. *J Clin Neuroophthalmol* 3(3):211–220
- Green AJ et al (2010) Ocular pathology in multiple sclerosis: retinal atrophy and inflammation irrespective of disease duration. *Brain* 133(Pt 6):1591–1601
- Oberwahrenbrock T et al (2013) Retinal ganglion cell and inner plexiform layer thinning in clinically isolated syndrome. *Mult Scler* 19(14):1887–1895
- Brandt AU et al (2011) Primary retinal pathology in multiple sclerosis as detected by optical coherence tomography. *Brain* 134(Pt 11):e193 (author reply e194)
- Balcer LJ et al (2015) Vision and vision-related outcome measures in multiple sclerosis. *Brain* 138(Pt 1):11–27