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Visual Function and Brief Cognitive Assessment for Multiple Sclerosis in Optic Neuritis Clinically Isolated Syndrome Patients

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Background: In this study, we hypothesized that clinically isolated syndrome–optic neuritis patients may have disturbances in neuropsychological functions related to visual processes.

Methods: Forty-two patients with optic neuritis within 3 months from onset and 13 healthy controls were assessed at baseline and 6 months with MRI (brain volumes, lesion load, and optic radiation lesion volume) and optical coherence tomography (OCT) (peripapillary retinal nerve fiber layer [RNFL], ganglion cell and inner plexiform layers [GCIPLs], and inner nuclear layer). Patients underwent the brief cognitive assessment for multiple sclerosis, high-contrast and low-contrast letter acuity, and color vision.

Results: At baseline, patients had impaired visual function, had GCIPL thinning in both eyes, and performed below the normative average in the visual-related tests: Symbol Digit Modalities Test and Brief Visuospatial Memory Test-Revised (BVMT-R). Over time, improvement in visual function in the affected eye was predicted by baseline GCIPL (P = 0.015), RNFL decreased, and the BVMT-R improved (P = 0.001). Improvement in BVMT-R was associated with improvement in the high-contrast letter acuity of the affected eye (P = 0.03), independently of OCT and MRI metrics.

Conclusion: Cognitive testing, assessed binocularly, of visuospatial processing is affected after unilateral optic neuritis and improves over time with visual recovery. This is not related to structural markers of the visual or central nervous system.

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Optic neuritis (ON) is a frequent presentation of demyelinating clinically isolated syndrome (CIS) (1). Research studies often include cognitive outcomes when investigating disability accrual and risk for multiple sclerosis (MS) conversion in CIS cohorts. Although most studies have found deficits in information processing speed and visuospatial memory (2–4), the prevalence of cognitive impairment in CIS patients varies from one study to another (5). One explanation is that researchers do not always assess vision and damage in the visual pathways when testing cognition in CIS patients with ON. In this study, we hypothesize these factors can influence vision-dependent cognitive tests in ON-CIS patients.

MS researchers have shown relationships between visual function and cognitive performance, for tests depending on visual (6–10) and nonvisual inputs (8–10). However, these studies included heterogeneous cohorts for past ON history (6–10). Furthermore, they assessed patients with long disease duration (9,10) and other MS phenotypes (i.e., relapsing–remitting and progressive). Therefore, they may have observed the effects of the central nervous system (CNS) damage accrual on both vision and cognitive functions.

Markers of retinal damage derived from optical coherence tomography (OCT), namely, peripapillary retinal nerve fiber layer (pRNFL) and combined ganglion cell and inner plexiform layers (GCIPLs), have inconsistent associations with cognitive outcomes (9–14). Some studies included patients with a previous ON (9,10,14). Hence, their findings may have been affected by pre-existing retinal layer changes. Other studies excluded eyes with previous ON (11,13), but, by including patients with long disease duration, and other factors, such as brain atrophy or white matter (WM) lesion accrual, may have influenced their results. A recent study (12) grouped the patients according to the ON history and reported an association between GCIPL thinning and cognitive impairment evident only in the group without a history of ON.

In this study, we studied only patients with unilateral ON-CIS and analyzed affected (AEs) and nonaffected eyes (NAEs) separately. We assessed patients within 3 months after the onset of ON and at 6 months, after visual recovery (15), and when ON-related retinal thinning is evident (16,17). We used MRI to evaluate the possible contribution of damage to the posterior visual pathways and the CNS. We chose the brief cognitive assessment for MS (BICAMS) (18) because it includes visually and nonvisually dependent tests.

METHODS

We recruited 42 patients with ON within 3 months from onset, from the National Hospital of Neurology and Neurosurgery and the Moorfields Eye Hospital, London, United Kingdom. Exclusion criteria were a history of past neurological episodes or previous ON episodes, antibodies against aquaporin-4 and myelin oligodendrocyte glycoprotein (routinely assessed), other medical conditions potentially affecting the CNS, including cardiovascular risk factors, and the eye, and high refractive errors (>-6.0 or +6.0 D). We also recruited 13 healthy controls (HCs).

Clinical assessments (patients alone), OCT, and MRI were performed at baseline and after 6 months.

All subjects gave written informed consent (Study Ref: 13/LO/1762; 13/0231-CIS2013).

We scored physical disability using the Expanded Disability Status Scale. For visual function, we assessed each eye separately. We scored: high-contrast letter acuity (HCLA) using logMAR high contrast (100%) Early Treatment Diabetic Retinopathy Study charts at 4 m, low-contrast letter acuity (LCLA) (2.5% and 1.25%) as the total number of letters read correctly using Sloan letter charts at 2 m, and the color vision as the total error score (TES) at the Farnsworth–Munsell test (19).

We used BICAMS that includes the Symbol Digit Modalities Test (SDMT) for information processing speed, the California Verbal Learning Test-II (CVLT-II) for verbal memory, and the Brief Visuospatial Memory Test-Revised (BVMT-R) for visuospatial memory.

We recorded years of education for each patient and calculated z-scores using the data set provided by the BICAMS initiative (https://www.bicams.net) (20). In all tests, participants used their habitual distance corrective lenses. For HCLA, subjects also used pin-hole correction with their habitual lenses, and we used the best-corrected scores.

We used spectral-domain OCT (Spectralis v.1.7.1.0, Heidelberg Engineering) with eye tracking for measurement accuracy (21) without pharmacological pupil dilatation. For each eye, we acquired 1) three 3.4 mm peripapillary circular scans (automatic real time [ART] 100) manually centered around the optic nerve with the highest quality chosen for analysis and 2) a macular volume scan—we manually centered the scan around the fovea (vertical alignment, ART 10–25). We used the baseline peripapillary and macular scans as references for the follow-up scans.

We obtained individual macular layers with an automated segmentation software (HRA/Spectralis Viewing Module version 5.6.4.0). We performed quality control (QC) according to OSCAR-IB criteria (22) and excluded the scans failing the QC. In the case of minor failures of the automated segmentation, whenever possible, we performed manual correction.

For pRNFL thickness, we used the global average of the thickness. We used a 1–3–6 mm grid on the thickness map for the macular scan, selecting the 1–3-mm ring values for our analysis. We combined the ganglion cell layer and the inner plexiform layer in the GCIPL (23), and we recorded the values of the inner nuclear layer.

For each subject, we used the OCT measurements from each eye.

We used a 3T Philips Achieva system (Philips Medical Systems, Best, Netherlands).

The MRI protocol included 2D short-tau inversion-recovery coronal sequences of the orbits; 3D T1-weighted turbo field echo, 3D fluid-attenuated inversion recovery, and 2D proton density (PD)/T2-weighted turbo spin-echo of the brain; sagittal PD/T2-weighted images of the spinal cord; and pregadolinium and postgadolinium T1-weighted imaging of the orbits, brain, and spinal cord (patients at baseline alone).

We determined lesion dissemination in space and time according to the revised 2017 McDonald criteria (24) for MS diagnosis.

We outlined WM lesions on the 2D PD/T2-weighted images using JIM v6.0 (Xinapse systems) and computed lesion volumes.

The lesion masks were coregistered to the 3D-T1 images (25) for lesion filling (26). Subsequently, we used Geodesic Information Flows (27) for brain extraction and tissue segmentation.

At baseline, after registering the 3D-T1 images in the Montreal Neurological Institute (MNI152) space, we used the Juelich Histological Atlas (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases/Juelich) to create binary optic radiation masks. We then obtained the volume of the lesions in the optic radiations.

We assessed the percentage of brain volume change (PBVC) with SIENA (28).

We assessed group differences between CIS-ON patients and HCs for demographic characteristics using the 2-sample *t* test for continuous variables and the chi-square test for categorical variables.

We conducted 3 statistical analyses.

1. At baseline, group differences in brain volumes and brain parenchymal fraction (BPF) were assessed with linear regression adjusting for age and sex.

We used mixed effect models to assess the differences in OCT metrics between patients' NAEs and HCs' eyes adjusting for age, sex, months from onset, ethnicity (categorized as Caucasian and non-Caucasian). We also tested the effect of lesion volumes (WM and optic radiation) and BPF on the model.

In patients, we used the same model for the differences in OCT metrics and visual outcomes between patients' AEs and NAEs adjusting for steroid treatment at the onset.

1. For the longitudinal analysis, group differences in PBVC were assessed with linear regression adjusting for age and sex.

We used mixed effect models to assess differences in changes over time in OCT metrics between patients' NAEs and HCs' eyes adjusting for age, sex, and months from onset. However, we also added time and group × time interaction as explanatory variables. If significantly different, PBVC was added to the model.

In patients, we used a similar model to assess the difference between eyes in changes in visual outcomes and OCT metrics.

In patients, a similar model, not stratified by eyes, was used for BICAMS scores, also adjusting for education. We used raw scores as they attain the same significance level of z-scores (20), whereas we used Z-scores for descriptive purposes.

If a variable x showed a significant change over time, we calculated the difference between 6 months and baseline (labeled as Δx). We used the Δvariables in the subsequent analysis.

1. We applied multiple linear regression models, adjusted for age and sex, to assess the effects of OCT metrics, MRI parameters, and visual scores on cognition.

At baseline, each cognitive score was entered separately as a response variable. Predictors were OCT metrics, if significantly different between patients and controls or between AEs and NAEs, and visual outcomes, if significantly different between patients' eyes. We also explored the effect of BPF and lesion volume on the model.

For the longitudinal model, we entered only significant Δ cognitive scores as response variables in the model. The significant ΔOCT metrics and Δvisual outcomes were entered separately as predictors. We explored the effect of PVBC and lesion volume change on the model.

Statistical analyses were performed with Stata v.14.1 (Stata Corporation, College Station, TX).

Only results associated with $P < 0.05$ were considered statistically significant and subsequently reported in this article. Because of the exploratory nature of the study, correction for multiple comparisons was not performed.

RESULTS

Thirty patients and 13 HCs completed the study at 6 months. Patients and HCs did not differ significantly for age, sex, brain volumes, and PBVC (Table 1). None of the patients had comorbidities or were taking treatments altering their mental states.

Thirty-six (86%) of 42 baseline CIS patients presented with brain lesions and 30 of them had lesions involving the optic radiations (Table 2).

After quality control of OCT acquisitions, we discarded the following patients' OCT data: 9/84 (11%) baseline and 4/60 (7%) 6-month pRNFL; 8/84 (10%) baseline and 3/60 (6%) 6-month macular scans. HCs' OCT scans passed the QC.

The AE GCIPL was significantly lower than NAE GCIPL (coeff. = −11.5 μm, $P < 0.0001$), which was lower than in HCs (coeff. = −7.7 μm, $P = 0.002$) (Fig. 1). The

TABLE 1. Demographic characteristics and brain volumes of patients and healthy controls at baseline

	Patients	HCs	*P*
N	42	13	—
Age, yrs, mean (SD)	33 (7)	33 (6)	0.78*
Sex, N female (%)	25 (60)	7 (54)	0.88†
Ethnicity, N (%)			
Caucasian‡	31 (74)	30 (94)	0.019†
Black‡	3 (7)	0	—
Asian‡	6 (14)	0	—
Chinese	0	0	—
Mixed	1 (2)	0	—
Others	1 (2)	2 (6)	—
Months from onset, mean (SD)	2 (1.2)	—	—
White matter vol. mL, mean (SD)	450 (38)	467 (50)	0.12§
Deep gray matter vol. mL, mean (SD)	37 (3)	38 (3)	0.19§
Cortical gray matter vol. mL, mean (SD)	627 (46)	634 (62)	0.98§
Brain parenchymal fraction, mean (SD)	0.76 (0.009)	0.76 (0.01)	0.64§
6-month brain volume change %, mean (SD)	−0.018 (0.7)	0.04 (0.7)	0.22‖

*Two-sample *t* test.
†Chi-square test.
‡Caucasian: English/Irish or other Caucasian background; Asian: Indian/Pakistani/Bangladeshi or another Asian background; Black: Caribbean, African, or other Black background.
§Linear regression adjusting for age and sex.
‖Linear regression adjusting for age and sex.
HCs, healthy controls; Gm, gray matter; ORs, optic radiations; Wm, white matter; vol., volume.

TABLE 2. Clinical and MRI characteristics of patients at baseline and 6 months

	Baseline	6 Months	*P*
N	42	30	—
Months from onset, mean (SD)	2 (1.2)	—	—
Visual acuity at onset, logMar mean (SD)	0.6 (0.7)	—	—
MS,* N (%)	9 (21)	11 (37)	—
T1-isointense lesion vol. mL, mean (SD)	6.2 (8.5)	6.2 (8.3)	0.98†
T1-hypointense lesion vol. mL, mean (SD)	0.6 (1.1)	—	—
Optic radiations lesion vol. mL, mean (SD)	0.4 (0.6)	—	—
Total lesion number, median (IQR)	16 (59)	13 (62)	—
EDSS, median (IQR)	1.5 (0.5)	1 (1.5)	—
Steroids, N (%)	15 (36)	0 (0)	—
DMDs, N (%)	0 (0)	7 (30)	—
CVLTII, mean (SD)			
Raw score	60.6 (9)	67 (6)	0.01§
Z-score‡	1.2 (1.2)	2.08 (1)	—
SDMT mean (SD)			
Raw score	57.9 (9.3)	59.7 (8.5)	0.32§
Z-score‡	−0.86 (1.1)	−0.55 (0.6)	—
BVMT-R mean (SD)			
Raw score	25.6 (5.4)	28.4 (3.1)	0.001§
Z-score‡	−0.39 (1)	0.17 (1)	—

*Multiple sclerosis diagnosed according to McDonald Criteria 2017 revision.
†Paired *t* test.
‡Z-scores (age-adjusted, sex-adjusted, and education-adjusted) were calculated using the data set provided by the BICAMS initiative (https://www.bicams.net) (17).
§Mixed effect model adjusted for age, sex, education, and months from onset.
BVMT-R, Brief Visuospatial Memory Test-Revised; CVLTII, California Verbal Learning Test II; DMDs: disease modifying drugs; EDSS, Expanded Disability Status Scale; IQR, inter-quartile range; MS, multiple sclerosis; SDMT, Symbol Digit Modalities Test.

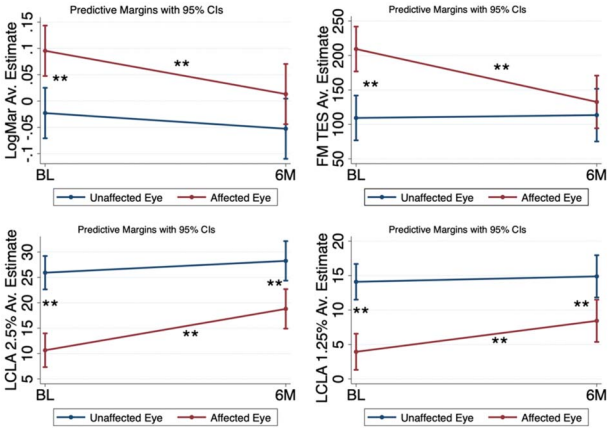

FIG. 1. Visual outcomes. $^{**}P < 0.0001$. Results from mixed effect models adjusted for age, sex, steroids intake, and months from onset. For changes overtime, an interaction group x time was used. Av, average; BL, baseline; 6 M, six months; FM, Farnsworth–Munsell test; TES, total error score; LCLA, low-contrast letter acuity.

GCIPL in the NAEs was not associated with the lesion volumes or BPF.

AEs had significant deficits for HCLA (coeff. = 0.12 logMAR, $P < 0.0001$), 2.5% and 1.25% LCLA (coeff. = −15.3 and coeff. = −10.2 letters, respectively; $P < 0.0001$), and color vision TES (coeff. = 100, $P < 0.0001$) compared with NAEs (Fig. 2).

At baseline, although all patients performed in the normative average for CVLTII, 10 (24%) patients and 4 (10%) showed deficits (<1.5 z-score) for SDMT and BVMT-R, respectively. Two (5%) patients had <1.5 z-score in both tests matching the definition for cognitive impairment (Table 2; Fig. 3).

The pRNFL decreased significantly in the AEs (coeff. = −13.05 logMAR, $P = 0.02$), whereas the GCIPL did not change significantly (Table 3, Fig. 2).

All the visual scores in the AEs improved (Table 3, Fig. 1). The LCLA 1.25% improvement was predicted by thicker baseline GCIPL in the AEs (RC [95% CIs]: 0.33 letter/μm, [0.07, 0.58], $P = 0.015$) (Table 4; Fig. 1).

Baseline BICAMS scores correlated neither with BPF, brain, and lesion volumes (See **Supplemental Digital Content 1**, Table E1, http://links.lww.com/WNO/A466) nor with visual and OCT metrics.

PVBC and lesion volume change did not correlate with ΔBVMT-R and ΔCVLTII (See **Supplemental Digital Content 2**, Table E1, http://links.lww.com/WNO/A466).

The improvement in the BVMT-R score was significantly associated with the improvement in the AE HCLA ($R^2 = 0.17$; B = −19.9; 95 CI = −38.3 to −1.5, $P = 0.03$) (Fig. 4). The PBVC did not affect the significance of the correlation ($P = 0.045$), whereas the lesion volume change did ($P = 0.07$). PVBC and lesion volume change did not affect the other correlations between ΔBVMT-R and ΔCVLTII and Δvisual and ΔOCT parameters.

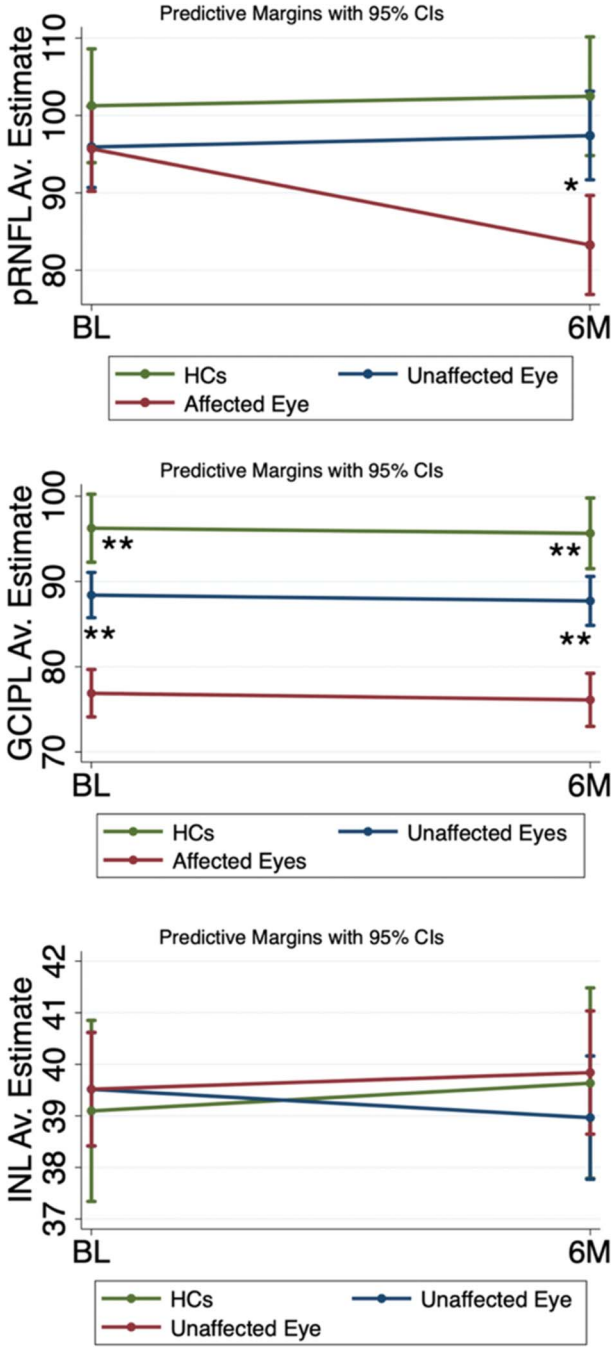

FIG. 2. Optical coherence tomography metrics. $^{**}P < 0.0001$ $^{*}P < 0.05$. Results from mixed effect models adjusted for age, sex, steroids intake, and months from onset. For changes overtime, an interaction group x time was used. Av, average; BL, baseline; 6 M, 6 months; pRNLF, peripapillary retinal nerve fiber layer; GCIPL, combined ganglion cell and inner plexiform layers; INL, inner nuclear layer.

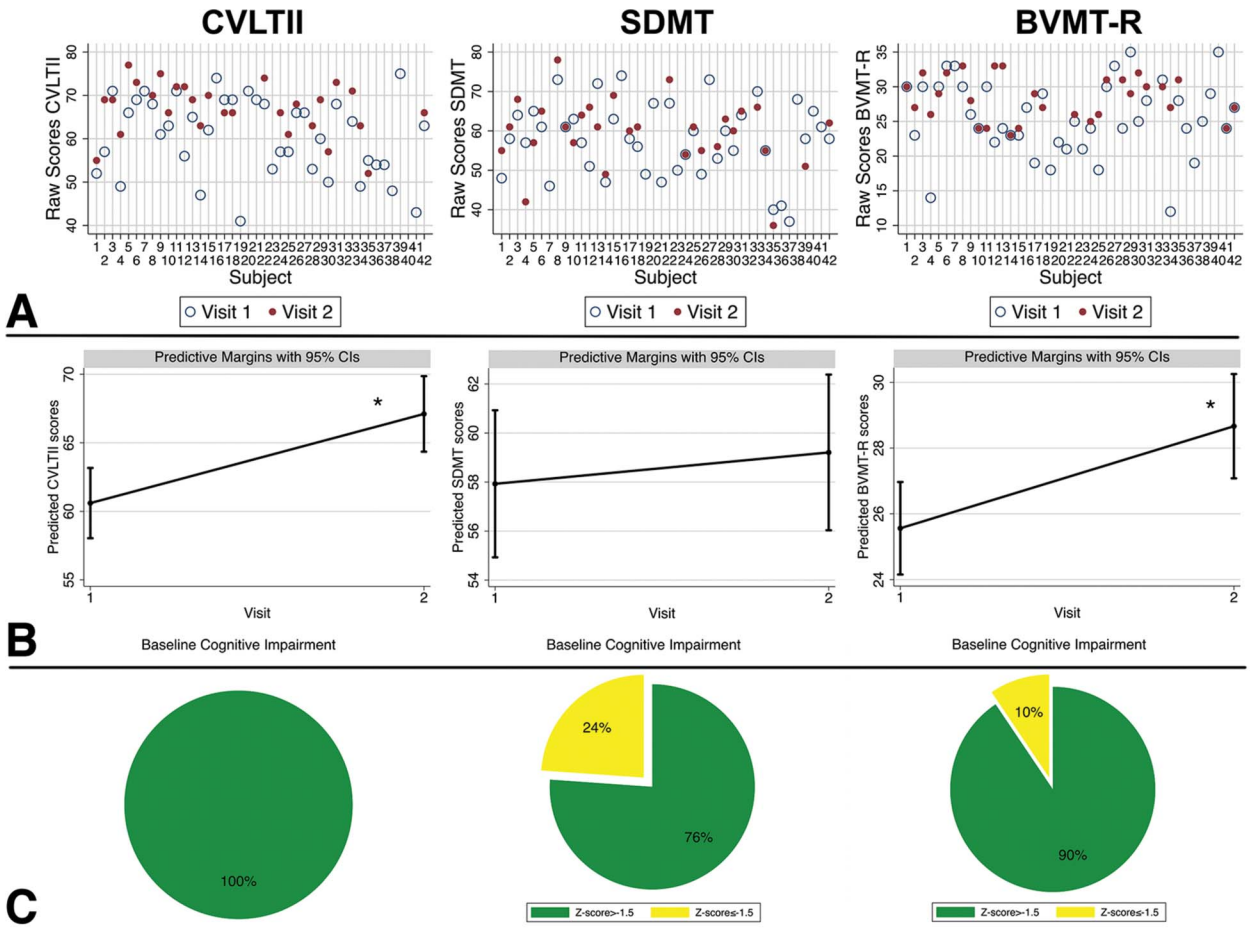

FIG. 3. Cognitive outcomes in patients. *$P < 0.05$. **A**. Scatter plot of cognitive test scores for each subject and each time point (**B**) results from mixed effect models adjusted for age, sex, and months from onset; (**C**) prevalence of cognitive impairment (defined as z-score <-1.5) in the cognitive tests at baseline. BVMT-R, brief visuospatial memory test-revised; CVLTII, California verbal learning test II; SDMT, Symbol Digit Modality Test.

CONCLUSION

Patients with clinically isolated, unilateral ON performed worse in BICAMS visually dependent tests (BVMT-R and SDMT) than in nondependent (CVLTII). Over time, both the CVLTII and BVMT-R had an improvement possibly influenced by the general relapse recovery.

We did not find correlations between these changes and most of our visual outcomes. However, the BVMT-R improvement was associated with the recovery of visual function (HCLA). We believe this result is of clinical interest, particularly as it was independent from brain atrophy.

The correlation between BVMT-R improvement and AE HCLA recovery is interesting as the NAE remains visually noncompromised. It is possible, however, that higher visual processing, tested in this study by BVMT-R, depends on binocular afferent stability and/or symmetry. When this is disrupted, there is impairment of visually dependent cognitive performance. As the AE improves, binocular visual symmetry is restored and visual cognitive performance normalizes. Lesion accumulation may have an impact on this process. The mechanisms for this are speculative but may include higher visual neuroplastic changes. Furthermore, bidirectional relationships between vision and cognition may occur (9).

LCLA, although recovering significantly, remained impaired in patients' AEs, but we could not find correlations with SDMT or BVMT-R, in contrast to previous studies (9,10). These studies, however, showed a correlation between LCLA and cognition, independently of the ON history. As LCLA has been related to CNS damage (29), particularly global and regional brain atrophy (30), in MS patients with long disease duration, LCLA may be related to cognitive performance as a surrogate marker of neurodegeneration and not just of visual impairment. This would also explain similar results in neurodegenerative diseases (31,32). In our cohort, instead, in the absence of brain atrophy, LCLA could reflect visual pathway damage more than CNS alterations, as shown by the correlation with GCIPL.

TABLE 3. Optical coherence tomography metrics in patients and healthy controls

Metrics		Affected Eye	Nonaffected Eye	Coeff. (95% CI)	*P**	HCs	Coeff. (95% CI)	*P*†
pRNFL	BL μm, mean (SD)	95.4 (30.5)	95.4 (12.7)	0.3 (−7.3, 7.9)	0.93	101.7 (9.9)	−5.9 (−13 to −1.3)	0.11
	6M μm, mean (SD)	81.2 (13.8)	99.4 (11.4)	−14.7 (−23.6, −5.9)	0.001	101.6 (10.1)	−5.2 (−13.1 to 1.4)	0.12
	Coeff. (95% CI) BL vs 6M	−13.05 (−21.5 to −4.6)	2 (−6.4 to 10.3)	—	—	1.2 (−1.9, 4.2)	—	—
	P-value‡	0.02	0.65	—	—	0.46	—	—
GCIPL	BL μm, mean (SD)	76.8 (10.2)	88.4 (8.6)	−11.5 (−14.8, −8.2)	<0.0001	96.4 (7)	−7.7 (−12.7 to −2.8)	0.002
	6M μm, mean (SD)	75.3 (12.5)	90.7 (8.9)	−11.8 (−15.6, −7.9)	<0.0001	95.7 (9.4)	−8.4 (−13.5 to −3.3)	0.001
	Coeff. (95% CI) BL vs 6M	−0.7 (−4.4 to 3)	−0.44 (−4.1 to 3.2)	—	—	−1.4 (−3.1, 0.4)	—	—
	P-value‡	0.72	0.81	—	—	0.13	—	—
INL	BL μm, mean (SD)	39.4 (3.3)	39.5 (3.6)	0.003 (−0.8, 0.8)	0.98	39 (3)	0.4 (−1.6 to 2.4)	0.68
	6M μm, mean (SD)	39.7 (4)	39 (3.6)	0.9 (−0.08, 1.8)	0.07	39.7 (3.7)	−0.8 (−3 to 1.4)	0.46
	Coeff. (95% CI) BL vs 6M	0.4 (−0.6 to 1.3)	−0.5 (−1.4, 0.4)	—	—	0.6 (−0.8, 2)	—	—
	P-value‡	0.45	0.29	—	—	0.38	—	—

*Mixed effect model adjusted for age, sex, steroids months from onset, and steroids comparing affected eyes and nonaffected eyes.
†Mixed effect model adjusted for age, sex, and months from onset comparing patients' nonaffected eyes with the average of healthy controls eyes.
‡Mixed effect model adjusted for age, sex, steroids, and months from onset comparing baseline with 6-month values.
BL, baseline; GCIPL, combined ganglion cell and inner plexiform layers; HCs, healthy controls; pRNFL, peripapillary retinal nerve fiber layer; INL, inner nuclear layer.

TABLE 4. Visual outcomes in patients

Metrics		Affected Eye	Nonaffected Eye	Coeff. (95% CIs)	*P**
HCLA	BL LogMar, mean (SD)	0.1 (0.2)	−0.02 (0.1)	0.12 (0.06 to 0.18)	<0.0001
	6M LogMar, mean (SD)	0.04 (0.2)	−0.06 (0.1)	0.06 (−0.007 to 0.14)	0.08
	Coeff. (95% CI)	4.5 (0.6 to 8.4)	0.8 (−3.04 to 4.7)	—	—
	P-value†	0.023	0.68	—	—
LCLA 2.5%	BL, mean (SD)	11 (12)	26 (11)	−15.3 (−19.6 to −10.9)	<0.0001
	6M, mean (SD)	17 (12)	28.6 (7.9)	−9.4 (−14.6 to −4.3)	<0.0001
	Coeff. (95% CI)				
	P-value†				
LCLA 1.25%	BL, mean (SD)	4 (7)	14 (11)	−10.1 (−13.6 to −6.7)	<0.0001
	6M, mean (SD)	8 (8)	15 (8.5)	−6.5 (−10.6 to −2.3)	0.002
	Coeff. (95% CI)	8.2 (3.3, 13)	2.3 (−2.5, 7.2)	—	—
	P-value†	0.001	0.34	—	—
TES	BL, mean (SD)	209.4 (176)	109.4 (56.6)	100 (58.3 to 141.7)	<0.0001
	6M, mean (SD)	129 (178.5)	108.3 (56.7)	41.4 (−4.4 to 87.1)	0.08
	Coeff. (95% CI)	−59.6 (−103.8 to −15.3)	0.9 (−45.2 to 43.3)	—	—
	P-value†	0.008	0.97	—	—

*Mixed effect model adjusted for age, sex, months from onset and steroids comparing affected eyes and non-affected eyes.
†Mixed effect model adjusted for age, sex and months from onset and steroids comparing baseline with 6-month values.
CI, confidence interval; HCLA, high-contrast letter acuity; LCLA, low-contrast letter acuity; TES, total error score.

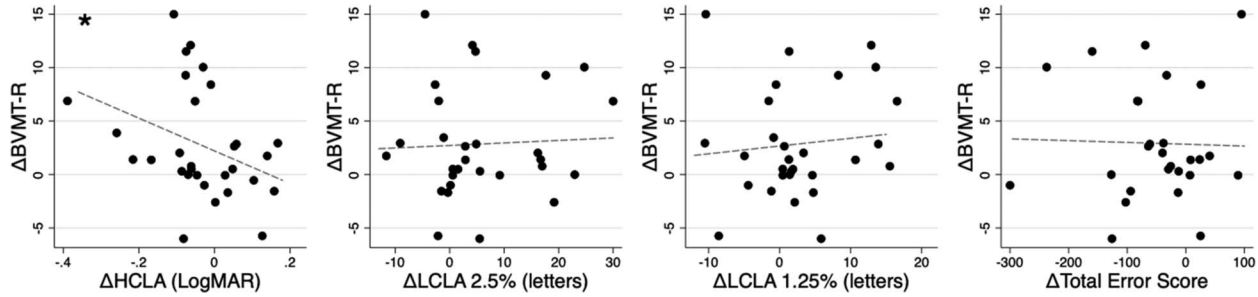

FIG. 4. Scatter plots of Δ bvmt-r and Δvisual scores in the affected eyes. *$P < 0.05$ results from linear regression adjusted for age, sex, education, and months from onset. BVMT-R, Brief Visuospatial Memory Test-Revised; FM TES, Farnsworth–Munsell total error score; HCLA, high-contrast letter acuity; LCLA, low-contrast letter acuity.

We found no associations between BICAMS scores and OCT metrics. The presence of demyelination, inflammation, and neuroaxonal damage at baseline may have different and possibly opposing effects on OCT masking potential correlations with BICAMS. Longitudinal studies are required to assess if, with the disease progression, relationships arise.

Finally, SDMT did not improve over time. Deficits in information processing speed are known to characterize CIS cognitive impairment (5). SDMT did not correlate with visual function or damage to visual pathways. This suggests that other mechanisms, possibly related to brain function, drive SDMT performances, as previously shown in early CIS patients (33).

In NAEs, the GCIPL was thinner than in HCs eye. At present, there is no imaging gold standard for ON (34). Therefore, one hypothesis is that there was sub-clinical nerve involvement. As the GCIPL did not correlate with lesion volumes, this reduces the chances of trans-synaptic degeneration from optic radiations. As brain volumes were neither altered nor related to NAEs GCIPL, another hypothesis is that this thinner GCIPL may represent a manifestation of early MS neurodegeneration not yet detectable in the brain (Table 5).

Our Study Has Several Limitations

We lost 12 patients at follow-up. However, our missed data points were stochastic, so, using mixed effect models, we could adjust for the missing data.

We could not use a non-ON CIS cohort to assess the generalizability of our findings. However, ON is a frequent CIS onset, and we believe that our results may be of interest for neurologists and researchers assessing cognition in CIS patients.

For BICAMS, we did not account for practice effects. However, we assessed intracohort relationships between visual and cognitive metrics; the practice effect should not explain the associations between HCLA and BVMT-R changes.

The patients in our cohort had relatively high lesion volumes. However, we had excluded alternative diagnoses, such as aquaporin 4 and myelin oligodendrocyte Ab conditions. Furthermore, we explored the effect of lesion volume variability in the study.

TABLE 5. Associations between significant ΔBICAMS scores and significant ΔOCT metrics and Δvisual outcomes

Response Variable	Predictor	R^2	B Coefficient (CIs)	*P**
ΔCVLTII	AE ΔpRNFL	0.25	0.07 (−0.009 to 0.1)	0.87
ΔBVMT-R	AE ΔpRNFL	0.39	−0.06 (−0.1 to 0.003)	0.061
ΔCVLTII	ΔHCLA	0.22	−12 (−32.7 to 8.6)	0.24
ΔBVMT-R	ΔHCLA	**0.17**	**−19.9 (−38.3** to **−1.5)**	**0.03**
ΔCVLTII	ΔLCLA 2.5%	0.2	−0.1 (−0.3 to 0.1)	0.3
ΔBVMT-R	ΔLCLA 2.5%	0.12	0.02 (−0.2 to 0.2)	0.83
ΔCVLTII	ΔLCLA 1.25%	0.16	−0.03 (−0.4 to 0.3)	0.88
ΔBVMT-R	ΔLCLA 1.25%	0.12	−0.03 (−0.3 to 0.3)	0.23
ΔCVLTII	ΔTES	0.23	0.02 (−0.007 to 0.04)	0.15
ΔBVMT-R	ΔTES	0.13	−0.002 (−0.03 to 0.02)	0.84

P value significance for bold entries.

*Results are from linear regression models adjusted for age, sex, and education and months from onset.

AE, affected eye; BICAMS, Brief Cognitive Assessment for Multiple Sclerosis; BVMT-R,Brief Visuospatial Memory Test-Revised; CIs, confidence intervals; CVLT-II, California Verbal Learning Test-II; HCLA, high-contrast letter acuity; LCLA, low-contrast letter acuity; pRNFL, peripapillary retinal nerve fiber layer; SDMT, Symbol Digit Modalities Test; TES, total error score (Farnsworth–Munsell test).

Finally, the variable time from onset to recruitment among participants was another potential limitation. However, using for the first time MRI metrics to investigate the correlations between cognition and visual metrics, it is understandably challenging to assess patients at the exact onset of the ON.

In conclusion, our findings suggest that the visual acuity should be considered when BICAMS is administered to ON patients to interpret BVMT-R scores. This can have implications in clinical trials, where cognitive scores are often used, and vision is not measured.

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