Original Contribution

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Optical Coherence Tomography Is Associated With Cognitive Impairment in Multiple Sclerosis

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Background: Optical coherence tomography (OCT) is a sensitive method for quantifying retinal neuronal and axonal structures. Reductions in retinal nerve fiber layer (RNFL) and ganglion cell inner plexiform layer (GCIPL) thicknesses have a reported association with white and grey matter atrophy in multiple sclerosis (MS). We hypothesized that the thinning of intraretinal layer measurements associates with cognitive decline in MS patients with no prior event of optic neuritis (ON).
Methods: OCT and NeuroTrax computerized cognitive assessments were performed in 204 relapsing remitting MS patients with no history of ON or other conditions affecting the eye. Data were collected between 2010 and 2020 and retrospectively analyzed. Correlations were examined between cognitive performance and a lower RNFL or GCIPL thickness. A multilinear regression model was generated to assess the significance of these correlations regarding the disability score and disease duration.
Results: The 204 study participants had a mean age of 40.52 ± 11.8 years (mean ± SD) and disease duration of 9.80 ± 9.40 years. The mean RNFL thickness in this whole cohort was 82.22 ± 10.85 μm and the global cognitive score was 95.32 ± 12.32. The mean GCIPL thickness measured in a subgroup of 104 patients was 74.27 ± 10.37 μm. The RNFL and GCIPL both correlated with the global cognitive score (r = 0.174, $P = 0.013$ and r = 0.29, $P = 0.03$, respectively), and with various cognitive domains. However, the GCIPL showed stronger correlations than RNFL, particularly with executive function (r = 0.29, $P = 0.003$), attention (r = 0.332, $P = 0.001$), and the information processing speed (r = 0.25, $P = 0.012$). These correlations remained significant after correcting for confounders.
Conclusion: OCT measurements correlate with cognitive performance in MS patients. OCT can thus be used to evaluate central nervous system neurodegeneration in MS, as reflected by cognitive decline.

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Cognitive impairment is a major consequence of multiple sclerosis (MS) and further adversely affects the quality of life in affected patients. Cognitive decline may appear early in the disease process and has been reported even at the onset of MS (1). Indeed, prior modeling of the effects of cognitive impairment within the first year of MS onset has found that this decline begins at around 1.2 years before the appearance of clinical symptoms (2).

Much of the permanent cognitive decline experienced by MS patients is attributable to the axonal and neuronal degeneration that are secondary to inflammation and demyelination (3,4). Neuronal and axonal loss in MS are both fast and slow ongoing processes, leading to prominent brain atrophy and causing cognitive decline (5,6). Nonmyelinated axons in the anterior visual pathway, located anteriorly to the lamina cribrosa, act as a projection of the brain and are easy to examine, suggesting that measuring the ganglion cell-inner plexiform layer (GCIPL) and the retinal nerve fiber layer (RNFL) could shed light on the ongoing process of neurodegeneration in MS. Notably, both the GCIPL and RNFL thickness were reported previously to correlate with the white and grey matter volumes, brain parenchymal fraction, and cerebrospinal fluid

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volume in MS patients (7,8), and GCIPL atrophy was suggested to mirror the rates of global CNS processes (9). These findings suggest that assessments of unmyelinated retinal nerve fibers, which can be readily captured by optical coherence tomography (OCT), can be used to evaluate early cognitive decline in MS.

In the past decade, OCT has been thoroughly explored as a screening methodology in patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD) (10), and has revealed correlations between changes in RNFL thickness and/or volume, GCIPL degeneration, and cognitive decline. Moreover, GCIPL measurements were reported to be negatively correlated with disease duration in patients with mild AD (11), and an association between the RNFL thickness and continuous measures of cognitive ability has been described in various recent studies (12–14).

In accordance with the reported evidence to date, we speculated that OCT measurements would associate with cognitive decline in MS. We examined this possibility in our current study in MS patients with no evidence of past optic neuritis (ON) in either eye. These cases were chosen to avoid potentially misleading findings, because thinning of intraretinal layers could be the result of a previous event of ON, and not necessarily related to neurodegeneration in the entire brain. We aim to lay grounds for the possibility of using OCT as a biomarker of cognitive impairment in MS.

METHODS

Study Design and Patient Population

This was an observational study of patients diagnosed with MS that were followed between January 2010 and January 2020 in Sheba Multiple Sclerosis Center, Israel. Ethical approval to conduct the study was granted by the Sheba Medical Center Ethics Committee (IRB number 5596-08-SMC). All study subjects underwent spectral-domain OCT imaging with RNFL measurements for both eyes. A subgroup of patients underwent GCIPL measurements as well, and the eye yielding more prominent thinning was included in the statistical analysis, because it could better reflect the neurodegenerative process occurring in the brain. In addition, all study subjects completed a comprehensive cognitive assessment using the Neurotrax battery (15).

Inclusion criteria were as follows: (1) An MS diagnosis in accordance with the 2017 McDonald diagnostic criteria (16), including a brain MRI revealing typical demyelinating lesions; (2) a relapsing-remitting (RRMS) disease type; (3) normal visual acuity defined as a best-corrected visual acuity of $\geq$20/25 for both eyes, to avoid undocumented events of ON which affected visual acuity and could affect OCT measurements; and (4) cognitive and OCT assessments performed within 6 months of each other. Patients were excluded from the study if they satisfied any of the following: (1) a clinical history of ON, unilateral or bilateral; (2) known eye diseases for example, glaucoma, cataracts; or (3) the presence of any known systemic diseases that can affect the eye for example, diabetes, hypertension.

Demographic and clinical data were collected for all of the study subjects and included age, gender, years of education, disease duration, and disability status as measured by the Expanded Disability Status Scale (EDSS) (17). All subjects underwent comprehensive ophthalmologic tests including best-corrected visual acuity, intraocular pressure, color perception, pupillary light reflex, and a slit lamp examination of the anterior and posterior segments of both eyes.

Optical Coherence Tomography Measurements

Spectral-domain optical coherence tomography (SD-OCT) examinations were conducted using a Cirrus HD-OCT, model 4000 device, with version 6.0 software (Carl Zeiss Meditec, Jena, Germany) in all subjects to measure RNFL thickness, and GCIPL thickness in a subgroup of patients. The optic disc RNFL thickness was measured as an average thickness across 4 segments as follows: superior (120°), temporal (50°), inferior (120°), and nasal (70°). The average RNFL thickness was calculated also for the papillomacular bundle. The software for the Cirrus HD-OCT device maps all layers, including the 2 borders of the RNFL, and automatically calculates the thickness of the layers. The normal mean RNFL and GCIPL thicknesses are 100.6 ± 11.6 μm and 82.1 ± 6.2 μm, respectively, based on previous large-scale studies (18,19). We defined mild-to-moderate thinning as values at 1 SD below these normal levels, and severe thinning as values at 2 SD below these normal levels.

Cognitive Assessments

Cognitive performance in the study subjects was evaluated using a computerized cognitive test battery (Mindstreams; NeuroTrax Corp, New York, NY), designed to evaluate multiple cognitive domains including verbal and nonverbal memory, executive function, visual–spatial perception, verbal function, attention, information processing speed, and motor skills (15). A detailed description of this test battery, and explanation of the index scores used to designate the cognitive domains we tested, are available at http://www1.mindstreamshealth.com. The global cognitive score and each cognitive domain score for the study patients were standardized relative to age and education, stratified by cognitively intact norms, and scaled to an IQ-style scale (mean: 100, SD: 15). A value of 85 that is, 1 SD below normal, was designated as the cutoff for mild–moderate cognitive impairment, and a value of 70 that is, 2 SD below normal, as the cutoff for severe cognitive impairment.

Statistical Analysis

Statistical analyses were performed using IBM SPSS, version 25. Categorical variables were expressed as numbers and percentages and continuous variables as mean values with

SD, or minimum–maximum values, where appropriate. The 2-sample *t* test and the chi-squared test were used to compare continuous and categorical variables between groups respectively, divided according to a disease duration longer or shorter than 10 years. The normality of the distribution for continuous variables was confirmed with the Kolmogorov–Smirnov test. To evaluate correlations between measurements, the Pearson correlation coefficient was applied. The global cognitive score and its domains were considered dependent variables, whereas OCT measurements, EDSS, and disease duration were considered independent variables. A multivariate linear regression model using the stepwise approach was applied to simultaneously assess the effects of independent variables on a quantitative dependent variable. Only variables that were statistically associated were entered into the linear regression model. All tests applied were 2-tailed, and a *P*-value of 0.05 or less was considered statistically significant.

RESULTS

Patient Demographics and Clinical Characteristics

A total of 204 MS patients were included in the current study. The demographic and clinical characteristics of these subjects are presented in Table 1. RNFL thickness and cognitive performance were measured in all cases and the GCIPL was measured in 104 patients.

Intereye differences were found to be negligible (mean ± SD 5.33 ± 6.73 μm and 4.17 ± 9.69 μm for RNFL and GCIPL respectively), and therefore the eye yielding the lower result was included for each patient.

OCT results demonstrated a reduced thickness for both the RNFL and GCIPL in our MS cohort compared with the normal ranges. Seventy-seven patients (37.7%) showed mild-to-moderate RNFL thinning (RNFL ≤89 μm and >77.4 μm) and 74 cases (36.0%) displayed severe RNFL thinning (RNFL ≤77.4 μm). Twenty-five patients (24.0%) had mild-to-moderate GCIPL thinning (GCIPL≤ 75.9 μm and >69.7 μm) and 29 of our MS subjects (27.9%) had severe GCIPL thinning (GCIPL ≤69.7 μm). The global cognitive score was slightly reduced compared with the established normal levels. Twenty-six of our current MS patients (12.7%) presented with mild-to-moderate cognitive impairment (global cognitive score ≤85 and >70), and 13 patients (6.4%) with severe cognitive impairment (global cognitive score ≤70).

As expected, the MS patients in our present series with a longer disease duration were significantly older, had a higher degree of disability and more prominent RNFL and GCIPL thinning. In cognition, patients with a longer disease duration had a lower score than cases with more recent MS diagnosis across all domains, although only executive function, attention, and motor skills showed significant differences.

Correlation Between Optical Coherence Tomography Measurements and Cognitive Performance

OCT parameters significantly correlated with components of the cognitive assessment used in this present study. The RNFL thickness correlated with the global cognitive score, verbal function, attention, and motor skills. The GCIPL thickness correlated with the global cognitive score, executive function, attention, information processing speed, and motor skills. These results are detailed in Table 2 and demonstrated in Figure 1.

A multivariate linear regression model was used to examine whether the correlations found between OCT measures and cognition remained significant in the presence of the additional disease-related factors, EDSS, and disease duration. The results are detailed in Table 3, and the full models can be found in **Supplemental Digital Content 1** (**Table 1a–e**, http://links.lww.com/WNO/A485).

The R^2 of the model for global cognitive score was 0.187, demonstrating that 18.7% of the variance in the score could be explained, in descending order of influence, by the EDSS and the GCIPL thickness, as reflected by their standardized beta coefficients (Std β). Similarly, 28.2% of the variance in executive function could be explained by the EDSS and GCIPL measures, with 21.9% of the variance in attention attributable to these 2 variables. Regarding the information processing speed, 6.3% of the variance was explained by the GCIPL thickness alone.

Motor skills was the only domain in which the OCT data did not show a significant association. The model showed that 23.6% of the variance in that domain could be attributed solely to the EDSS. All of the beta coefficients showed significance of below 0.05. Finally, although the disease duration was found to be significantly associated with 3 different cognitive domains, this relationship did not prove to be significant in the presence of OCT measures and the EDSS value.

DISCUSSION

We have here analyzed a large cohort of RRMS patients for the correlation between OCT measures and cognitive performance. Because we aimed to isolate and explore the damage to the retina that could reflect the overall neurodegeneration in the brain, we applied strict criteria to include only patients with no previous history of ON or other eye disorders that could affect the thickness of either the RNFL or GCIPL. In spite of exclusion of this subgroup of patients, the cohort is characteristic of RRMS, showing episodes of inflammation excluding the eye. For cognitive assessments, we used an advanced comprehensive cognitive battery that enabled the evaluation of a wide range of cognitive domains, correcting for age and level of education, and including the response time into the calculated scores.

TABLE 1. Demographic and clinical characteristics of the study subjects

	All Subjects (N = 204)	Disease Duration ≤ 10 (N = 128)	Disease Duration >10 (N = 76)	*P*
Age, yrs	40.52 (11.8)	36.46 (10.91)	47.35 (9.98)	$P < 0.001$
Gender (%)				
Male	59 (28.9%)	41 (32.0%)	18 (23.7%)	0.207
Female	145 (71.1%)	87 (68.0%)	58 (76.3%)	
Disease duration, yrs	9.80 (9.40)	4.03 (3.02)	19.53 (8.43)	$P < 0.001$
Education, yrs	14.41 (2.5)	14.08 (2.51)	14.99 (2.39)	0.013
Expanded disability status scale	2.527 (1.81)	2.14 (1.55)	3.17 (2.03)	$P < 0.001$
Median (IQR)	2 (2)	2 (1.5)	2.5 (3.5)	$P < 0.001$
Retinal nerve fiber layer, μm	82.22 (10.85)	84.98 (10.06)	77.58 (10.62)	$P < 0.001$
Ganglion cell inner plexiform layer, μm	74.27 (10.37)	76.93 (10.01)	68.79 (8.95)	$P < 0.001$
Global cognitive score	95.32 (12.32)	96.49 (11.44)	93.36 (13.52)	0.079
Memory	96.20 (13.5)	96.4 (12.74)	95.87 (14.77)	0.787
Executive function	95.61 (13.87)	97.4 (12.73)	92.59 (15.21)	0.016
Visual spatial	100.32 (16.31)	100.77 (15.31)	99.56 (17.95)	0.612
Verbal function	93.84 (20.22)	93.92 (19.82)	93.68 (21.03)	0.937
Attention	94.66 (15.29)	96.64 (12.27)	91.36 (18.96)	0.032
Information processing speed	94.67 (17.07)	95.72 (17.15)	92.85 (16.89)	0.259
Motor skills	93.15 (19.66)	95.47 (18.45)	89.17 (21.12)	0.030
Immunomodulatory treatment				
Treated (%)	104 (50.9%)	68 (53.1%)	36 (47.4%)	0.432
Treatment duration, months	31.31 (44.97)	18.37 (21.35)	55.74 (64.34)	$P < 0.001$
Treatment type (% of patients treated)				
Dimethyl fumarate	26 (25%)	22 (32.3%)	4 (11.1%)	0.018
Interferon beta	25 (24%)	16 (23.5%)	9 (25%)	0.865
Fingolimod	20 (19.2%)	9 (13.2%)	11 (30.5%)	0.522
Natalizumab	14 (13.5%)	10 (14.7%)	4 (11.1%)	0.034
Teriflunomide	12 (11.5%)	11 (16.2%)	1 (2.7%)	0.041
Intravenous immunoglobulin	5 (4.8%)	3 (4.4%)	2 (5.5%)	0.803
Ocrelizumab	2 (1.9%)	0 (0%)	2 (5.5%)	0.052

Data are presented as a mean (SD) unless otherwise specified.

This provided an advantage over the manual cognitive assessments used in previous studies, which are less precise because they do not measure response time, and do not include all cognitive domains (2,20).

As expected, our current MS patients demonstrated reduced RNFL and GCIPL thicknesses than a previously reported age-matched healthy population, a recurrent finding in studies exploring MS subjects (21,22). Moreover, and similarly to our OCT findings, the cognitive performance of our MS cohort was below that expected for an age- and education-matched healthy population, thus demonstrating a mild decrease in cognitive functions. The most

TABLE 2. Correlations between optical coherence tomography parameters and cognitive performance

	RNFL		GCIPL	
	r*	*P*†	r	*P*
Global cognitive score	0.174	0.013	0.29	0.003
Executive function	0.133	0.058	0.35	$P < 0.001$
Visual spatial	0.114	0.107	0.14	0.16
Verbal function	0.169	0.016	0.189	0.056
Attention	0.164	0.019	0.332	0.001
Information processing speed	0.116	0.107	0.25	0.012
Motor skills	0.218	0.002	0.258	0.01
Memory	0.044	0.536	0.109	0.271

*r, correlation coefficient.
†$P < 0.05$ was considered significant.
GCIPL, ganglion cell inner plexiform layer; RNFL, retinal nerve fiber layer.

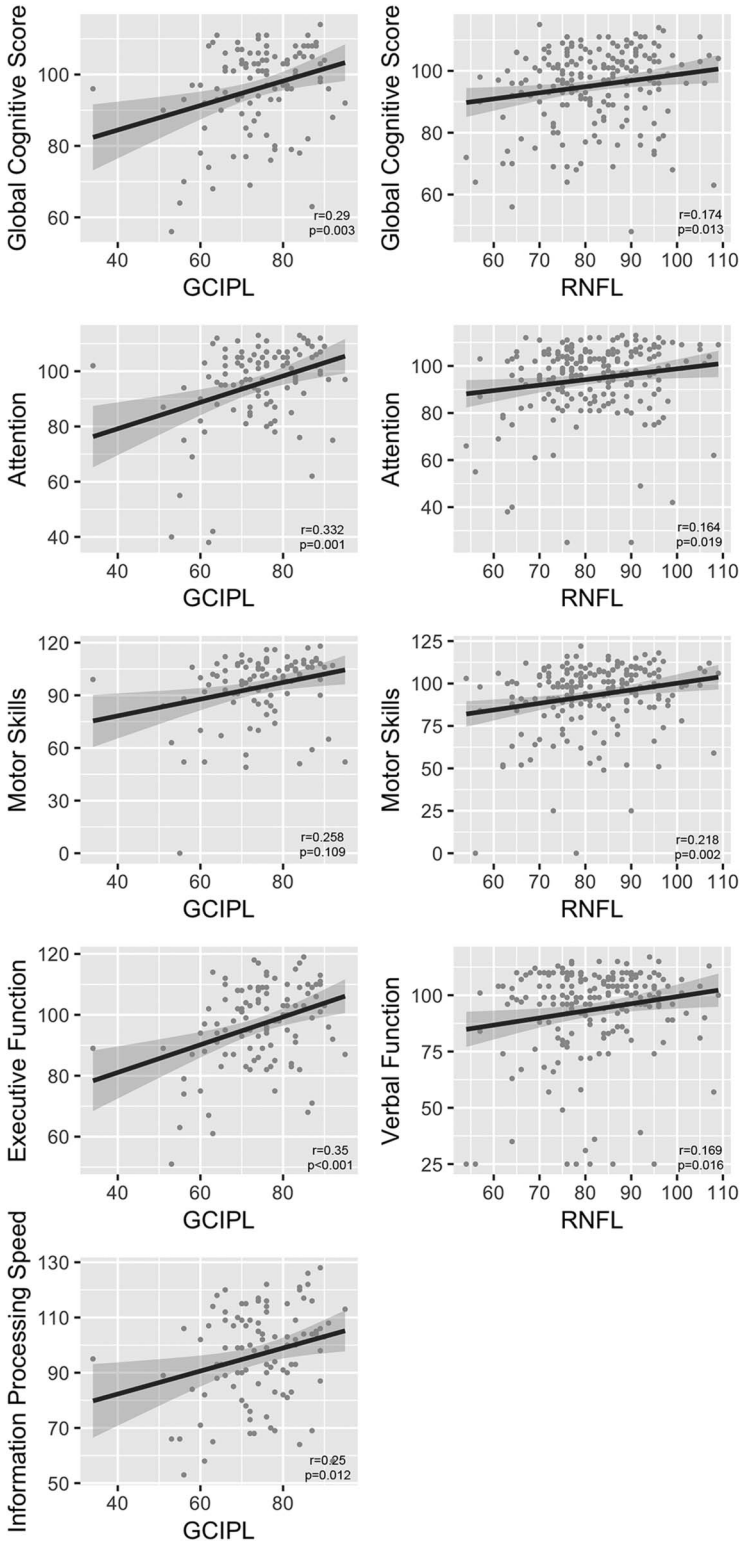

FIG. 1. Scatter plots of the statistically significant correlations between the retinal nerve fiber layer and ganglion cell inner plexiform layer thicknesses, and indicated cognitive domains.

prevalent impairment revealed in our current analyses was a decreased information processing speed, a finding consistent with that of previous studies (2,23).

The most notable findings of our current study were the correlations between OCT measures and various cognitive domains. Both the RNFL and GCIPL thicknesses measured

TABLE 3. Multivariate model for cognitive score and its components

		RNFL		GCIPL		EDSS		Disease Duration	
		Std β	*P*	Std β	*P*	Std β	*P*	Std β	*P*
Global cognitive score	$R^2 = 0.187$	—		0.216	0.021	−0.329	0.001	—	
Executive function	$R^2 = 0.282$	—		0.258	0.001	−0.41	$P<0.001$	—	
Attention	$R^2 = 0.219$	—		0.242	0.009	−0.342	$P<0.001$	—	
Information processing speed	$R^2 = 0.063$	—		0.25	0.012	—		—	
Motor skills	$R^2 = 0.236$	—		—		−0.485	$P < 0.001$	—	

Results are presented as standardized beta coefficient and *P*-value.
—, The variable did not significantly influence the model and therefore was excluded.
EDSS, expanded disability status scale; GCIPL, ganglion cell inner plexiform layer; RNFL, retinal nerve fiber layer.

in our present MS series significantly correlated with the global cognitive score, attention, and motor skills of these patients. The RNFL values additionally correlated with verbal function, whereas those for the GCIPL correlated with executive function and information processing speed. Significantly, these correlations remained after correcting for disease-related confounders including neurological disability and disease duration. Although the correlation coefficients were relatively low, especially for the RNFL relationship with the global cognitive score, albeit better for GCIPL thickness, we assume that decrease in intraretinal layer thickness may in part suggest a cognitive decline. Our findings are therefore in agreement with our suggested hypothesis that is, that the ongoing neurodegenerative process observed in the retina through OCT analysis in MS reflects that occurring in the brain. Hence, we suggest that axonal loss in the retina may be indicative also of cognitive decline and therefore possibly serve as an early biomarker for cognitive impairment in MS patients.

Consistent with our present findings, Toledo et al (24), Sadighi et al (25), and Ashtari et al (26), who studied MS cohorts of 52, 60, and 100 patients, respectively, found that the RNFL thickness correlated with either executive function or verbal function. A further prior study has evaluated the association between the GCIPL and cognition in 56 RRMS patients with no history of ON, and assessed cognition in these cases using the manual BRB-N examination (27). The authors demonstrated that the GCIPL measurements better correlated with cognitive domains than those for RNFL, particularly regarding executive function and visuospatial memory.

In our present analyses, we also found that the GCIPL thickness showed stronger correlations than that of the RNFL across various cognitive domains in MS patients. This was not a surprising finding, however, because the GCIPL includes the ganglion cell layer and its thinning signifies axonal loss, whereas the RNFL is formed by the expansion of the fibers of the optic nerve. As opposed to the optic nerve axonal counts, which are an accurate measure of the total number of ganglion cells in the retina, the RNFL thickness provides data on focal RNFL loss, and hence on focal ganglion cell loss. Hence, GCIPL measurements are a better biomarker for cognitive performance and are more specific than RNFL in assessing neurodegeneration in MS patients (22).

When examining the effect of MS disease duration on both OCT measures and cognitive function, it was unsurprising that the patients with the longer duration had a significantly thinner RNFL and GCIPL, reflecting a progressive neurodegeneration with the disease course. Cognitive function was found in our present observations to be partially associated with MS duration, showing significance in executive function, attention, and motor skills. However, when inserted into the multilinear regression model alongside OCT measures and the EDSS, the association between disease duration and cognition was not significant compared with other factors.

In our current model, the GCIPL thickness maintained its significant effect on the global cognitive score, executive function, attention, and information processing speed in the MS subjects. The OCT measures did not show a significant effect on motor skills when a correction for the EDSS was done, an unsurprising finding as this variable is a measure of disability and relates particularly to motor function. This provides further confirmation that OCT measures have a substantial relationship with cognitive function in MS, independent of the effect of disease duration, and that these associations are significant even in the presence of important predictors such as the EDSS.

The strength of our current study relates to the large cohort we enrolled and our strict exclusion criteria that were designed to avoid confounding factors, particularly those that could impair OCT measurements such as prior ON. Hence, we believe that the reductions we observed in both the RNFL and GCIPL thickness in MS are attributable solely to the neurodegenerative processes in this disease occurring at the retina, which parallel those manifesting in the brain.

The most significant drawback of our study was the relatively preserved cognitive performance of many of the subjects, which could have biased the findings. Only 19.1% of our study patients showed cognitive impairment, probably because of the relatively short disease duration in

this cohort, and thus only a minor proportion of our cohort contributed to the analysis. Despite this limitation however, the retinal thinning we observed in our MS patients, which appeared even in the cases with a short disease duration and preserved cognitive function, may suggest that this phenomenon, and especially GCIPL thinning, is an early biomarker of future cognitive decline in MS. Future studies that conduct a longitudinal assessment of these associations are warranted. Another potential limitation of our current analyses is the possibility that immunomodulatory treatment in most study cases had a beneficial effect in preventing cognitive decline, but with a lesser effect on retinal thinning.

To summarize, a decrease in RNFL and GCIPL thickness is associated with a decline in cognitive performance in MS patients. Although these OCT parameters do not fully explain the variations in cognitive performance in MS, they may serve as early biomarkers of cognitive decline and neurodegeneration in patients with this disease.

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REFERENCES

1. **Achiron A**, Barak Y. Cognitive changes in early MS: a call for a common framework. J Neurol Sci. 2006;245:47–51.
2. **Achiron A**, Chapman J, Magalashvili D, Dolev M, Lavie M, Bercovich E, Polliack M, Doniger GM, Stern Y, Khilkevich O, Menascu S, Hararai G, Gurevich M, Barak Y. Modeling of cognitive impairment by disease duration in multiple sclerosis: a cross-sectional study. PLoS One. 2013;8:e71058.
3. **Friese MA**, Schattling B, Fugger L. Mechanisms of neurodegeneration and axonal dysfunction in multiple sclerosis. Nat Rev Neurol. 2014;10:225–3838.
4. **Calabrese M**, Magliozzi R, Ciccarelli O, Geurts JJ, Reynolds R, Martin R. Exploring the origins of grey matter damage in multiple sclerosis. Nat Rev Neurosci. 2015;16:147–58.
5. **Amato MP**, Portaccio E, Goretti B, Zipoli V, Battaglini M, Bartolozzi ML, Stromillo ML, Guidi L, Siracusa G, Sorbi S, Federico A, De Stefano N. Association of neocortical volume changes with cognitive deterioration in relapsing-remitting multiple sclerosis. Arch Neurol. 2007;64:1157–6161.
6. **Harel Y**, Kalron A, Menascu S, Magalashvili D, Dolev M, Doniger G, Simon E, Achiron A. Cognitive function in multiple sclerosis: a long-term look on the bright side. PLoS One. 2019;14:e0221784.
7. **Sepulcre J**, Murie-Fernandez M, Salinas-Alaman A, García-Layana A, Bejarano B, Villoslada P. Diagnostic accuracy of retinal abnormalities in predicting disease activity in MS. Neurology. 2007;68:1488–9494.
8. **Gordon-Lipkin E**, Chodkowski B, Reich DS, Smith SA, Pulicken M, Balcer LJ, Frohman EM, Cutter G, Calabresi PA. Retinal nerve fiber layer is associated with brain atrophy in multiple sclerosis. Neurology. 2007;69:1603–1609.
9. **Ratchford JN**, Saidha S, Sotirchos ES, Oh JA, Seigo MA, Eckstein C, Durbin MK, Oakley JD, Meyer SA, Conger A, Frohman TC, Newsome SD, Balcer LJ, Frohman EM, Calabresi PA. Active MS is associated with accelerated retinal ganglion cell/inner plexiform layer thinning. Neurology. 2013;80:47–54.
10. **Doustar J**, Torbati T, Black KL, Koronyo Y, Koronyo-Hamaoui M. Optical coherence tomography in Alzheimer's disease and other neurodegenerative diseases. Front Neurol. 2017;8:701.
11. **Garcia-Martin E**, Bambo MP, Marques ML, Satue M, Otin S, Larrosa JM, Polo V, Pablo LE. Ganglion cell layer measurements correlate with disease severity in patients with Alzheimer's disease. Acta Ophthalmol. 2016;94:e454–e459.
12. **Oktem EO**, Derle E, Kibaroglu S, Oktem C, Akkoyun I, Can U. The relationship between the degree of cognitive impairment and retinal nerve fiber layer thickness. Neurol Sci. 2015;36:1141–1146.
13. **Bulut M**, Yaman A, Erol MK, Kurtuluş F, Toslak D, Doğan B, Turgut Çoban D, Kaya Başar E. Choroidal thickness in patients with mild cognitive impairment and Alzheimer's type dementia. J Ophthalmol. 2016;2016:7291257.
14. **Ascaso FJ**, Cruz N, Modrego PJ, Lopez-Anton R, Santabárbara J, Pascual LF, Lobo A, Cristóbal JA. Retinal alterations in mild cognitive impairment and Alzheimer's disease: an optical coherence tomography study. J Neurol. 2014;261:1522–3030.
15. **Simon ES**, Doniger GM; Inventors: NeuroTrax Corp, Assignee. Standardized medical cognitive assessment tool. United States Patent. 2007;7:294.
16. **Polman CH**, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, Fujihara K, Havrdova E, Hutchinson M, Kappos L, Lublin FD, Montalban X, O'Connor P, Sandberg-Wollheim M, Thompson AJ, Waubant E, Weinshenker B, Wolinsky JS. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011;69:292–302.
17. **Kurtzke JF**. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33:1444–1452.
18. **Budenz DL**, Anderson DR, Varma R, Schuman J, Cantor L, Savell J, Greenfield DS, Patella VM, Quigley HA, Tielsch J. Determinants of normal retinal nerve fiber layer thickness measured by Stratus OCT. Ophthalmology. 2007;114:1046–5252.
19. **Mwanza JC**, Durbin MK, Budenz DL, Girkin CA, Leung CK, Liebmann JM, Peace JH, Werner JS, Wollstein G. Profile and predictors of normal ganglion cell–inner plexiform layer thickness measured with frequency-domain optical coherence tomography. Invest Ophthalmol Vis Sci. 2011;52:7872–7879.
20. **Achiron A**, Doniger GM, Harel Y, Appleboim-Gavish N, Lavie M, Simon ES. Prolonged response times characterize cognitive performance in multiple sclerosis. Eur J Neurol. 2007;14:1102–1188.
21. **Talman LS**, Bisker ER, Sackel DJ, Long DA Jr, Galetta KM, Ratchford JN, Lile DJ, Farrell SK, Loguidice MJ, Remington G, Conger A, Frohman TC, Jacobs DA, Markowitz CE, Cutter GR, Ying GS, Dai Y, Maguire MG, Galetta SL, Frohman EM, Calabresi PA, Balcer LJ. Longitudinal study of vision and retinal nerve fiber layer thickness in multiple sclerosis. Ann Neurol. 2010;67:749–6060.
22. **Britze J**, Pihl-Jensen G, Frederiksen JL. Retinal ganglion cell analysis in multiple sclerosis and optic neuritis: a systematic review and meta-analysis. J Neurol. 2017;264:1837–1853.
23. **Heled E**, Aloni R, Achiron A. Cognitive functions and disability progression in relapsing-remitting multiple sclerosis: a longitudinal study. Appl Neuropsychol Adult. 2019;28:1–10.
24. **Toledo J**, Sepulcre J, Salinas-Alaman A, García-Layana A, Murie-Fernandez M, Bejarano B, Villoslada P. Retinal nerve fiber layer atrophy is associated with physical and cognitive disability in multiple sclerosis. Mult Scler. 2008;14:906–1212.
25. **Sedighi B**, Shafa MA, Abna Z, Ghaseminejad AK, Farahat R, Nakhaee N, Hassani B. Association of cognitive deficits with optical coherence tomography changes in multiple sclerosis patients. J Mult Scler. 2014;1:1–4.

26. **Ashtari F**, Emami P, Akbari M. Association between retinal nerve fiber layer thickness and magnetic resonance imaging findings and intelligence in patients with multiple sclerosis. Adv Biomed Res. 2015;4:223.

27. **Coric D**, Balk LJ, Verrijp M, Eijlers A, Schoonheim MM, Killestein J, Uitdehaag BM, Petzold A. Cognitive impairment in patients with multiple sclerosis is associated with atrophy of the inner retinal layers. Mult Scler. 2018;24:158–166.