

# Retinal measures correlate with cognitive and physical disability in early multiple sclerosis

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**Abstract** Further studies are needed to determine the role of retinal optical coherence tomography (OCT) in non-optic neuritis (ON) eyes of patients with early MS. The objective of this study is to explore the relationship between retinal layers' thickness and cognitive as well as physical disability in patients with the early RRMS. Participants in this cross-sectional study were adults with early RRMS, stable on interferon beta-1a, or fingolimod therapy, and without a history of ON in one or both eyes. Patients were evaluated clinically, underwent a battery of cognitive tests, and a retinal OCT scan which was also performed on a group of healthy age- and gender-matched controls. We studied 47 patients with RRMS, on interferon beta-1a ( $N = 32$ ) or fingolimod ( $N = 15$ ), and 18 healthy controls. Multivariate analyses controlling for age, disease duration, treatment, and education when exploring cognitive function, showed that pRNFL thickness correlated negatively with 9HPT (standardized Beta  $-0.4$ ,  $p < 0.0001$ ), and positively with SDMT (standardized Beta  $0.72$ ,

$p = 0.007$ ). In patients with early RRMS without optic neuropathy, retinal thickness measures correlated with physical disability and cognitive disability, supporting their potential as biomarkers of axonal loss.

**Keywords** Optical coherence tomography · Multiple sclerosis · Cognitive function · Physical disability · Retinal measures

## Introduction

Among the most important determinants of permanent disability in patients with multiple sclerosis (MS) are axonal loss and neurodegeneration [1], which result in both physical and cognitive impairment. Cognitive function is a critical aspect that needs to be closely monitored in patients with MS due to its direct impact on quality-of-life as well as its predictive value for disease progression [2, 3]. Cognitive dysfunction is a common problem in MS, and its prevalence has been estimated to be between 40 and 60 % [4]. The main fields of cognitive impairment in MS are information processing, memory, and spatial perception [5]. Extensive cognitive test batteries have been developed to consistently identify and monitor cognitive changes in MS. However, many of these tests have been confined to the research settings rather than routine clinical practice due to practicality issues and time constraints.

MRI is extremely useful in the diagnosis and follow-up of patients with MS, and is commonly used as a surrogate measure for outcomes of disease activity in clinical trials [6]. Furthermore, cerebral structural changes identified on MRI (as brain atrophy, a marker of axonal loss, and neurodegeneration in MS) showed a significant correlation with cognitive impairment [7]. However, non-invasive, less

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expensive, and more expeditious techniques to clinically monitor axonal loss in MS are being currently explored, such as examination of the retinal layers using OCT.

OCT is a method of optical signal acquisition and processing, employing near-infrared light that penetrates into the ocular medium and captures micrometer resolution, obtaining three-dimensional images from within optical scattering media (as biological tissue). Through OCT, it is possible to obtain subsurface images with a resolution equivalent to a low-power microscope. Hence, OCT can provide imaging of tissue morphology at much higher resolution (5–15  $\mu\text{m}$ ) than other modalities, such as MRI or ultrasound, being able to reliably measure the thickness of the peripapillary retinal nerve fiber layer (pRNFL), ganglion cell/inner plexiform layer (GCIPL), and macular volumes (MV).

pRNFL atrophy has been associated with disability and brain atrophy [8], which, in turn, has been associated with poor cognitive function in MS [5, 7, 9, 10]. Advances in segmentation techniques enabled the measurement of the GCIPL which correlates better with MS subtype [11] and has been associated with active MS [12]. However, OCT findings are not used as outcome measures in clinical trials, since more evidence is needed regarding the correlation of OCT findings with clinical outcomes, such as physical and cognitive disability, especially in patients with early MS. OCT might have the potential to be a non-invasive and practical technique to monitor axonal loss and neurodegeneration. In patients with early MS, monitoring for axonal loss is important, since prompt changes in their management could improve long-term outcomes and mitigate disability progression. Therefore, the main objective of this study is to explore the relationship between retinal OCT measures, cognitive function, and physical disability in patients with early MS.

## Methods

### Design and sample

This cross-sectional study was performed at the Nehme and Therese Tohme Multiple Sclerosis Center of the American University of Beirut Medical Center. The American University of Beirut Institutional Review Board approval was acquired, and written informed consent was obtained from all participants.

With a power of 80 % and two-sided significance level of 0.05, at least 52 eyes of RRMS participants (26 subjects) were needed to detect a minimum difference in GCIPL thickness of 0.4 standard deviations for each unit of change in the cognitive score given by the SDMT. Since around

30 % of MS suffer from optic neuritis, 21 more patients were recruited.

All patients who visited the MS center between January 2014 and December 2015 were evaluated for eligibility and invited to participate in this study. Eligible patients were adults diagnosed by the treating neurologist with relapsing-remitting multiple sclerosis based on the revised 2010 McDonald's criteria, disease duration of 5 years or less and clinically stable over the past 3 months, with no current optic neuritis (ON), and no history of ON in at least one eye, and on interferon or fingolimod therapy for more than 3 months. Patients were excluded if they had: progressive forms of MS, neuromyelitis optica spectrum disorders, diabetes mellitus, glaucoma, refractive errors of  $\pm 6$  diopters or more, other ophthalmologic disorders, such as media opacities, that may interfere with OCT measures, or other CNS disorders that may interfere with cognitive testing.

Age- and gender-matched healthy controls (HC) were identified among workers, students, and family members of the patients, invited to participate to obtain reference values of retinal layers' thickness. Healthy controls were eligible if they were aged between 18 and 55 years, with no history of demyelinating or neurodegenerative disorders, able to attend the scheduled study visits, and no history of diabetes mellitus, cerebrovascular disease, cognitive impairment, glaucoma, refractive errors of  $\pm 6$  diopters or more, or other ophthalmologic disorders that may interfere with OCT measures or any retinal pathology.

Clinical data collected included demographics, disease duration, number of MS attacks, disease modifying therapy, results of the previous visual evoked potentials (VEPs), and history of ON, in case it occurred in one eye only, including the date and side of occurrence. Participants with RRMS underwent clinical evaluation as per standards of care, including expanded disability status scale (EDSS) scores determined by the treating physicians, timed 25-foot walk test (T25FWT) in seconds, and 9-hole peg test (9HPT) in seconds. Since the dominant and non-dominant hand 9HPT scores were collinear in this sample, an average of the score of both hands was computed to represent the respective test score. The 9-HPT score was also used in the adjustment of the analysis of other cognitive tests that require motor skills (such as drawing). The Hopkins symptoms checklist-25 was administered to screen for a significant depression which could interfere with cognitive function testing.

### OCT scan

Eligible patients underwent retinal OCT scans in both eyes. Eyes with ON were excluded and only non-ON eyes were analyzed. Eyes with subclinical ON were excluded as well,

characterized by abnormal corrected visual acuity and abnormal VEPs, or baseline pRNFL thickness below the 25th percentile of the rest of participants. OCT measures included GCIPL thickness and pRNFL thickness in micrometers ( $\mu\text{m}$ ), and macular volumes in  $\text{mm}^3$ , measured by trained physicians at the MS center using the Cirrus HD-OCT (model 4000) device with software version 6.5 (Carl Zeiss Meditec, Dublin, CA). Peripapillary data were retrieved with the Optic Disc Cube  $200 \times 200$  protocol. Macular data were obtained with the Macular Cube  $512 \times 128$  protocol. Scans with signal strength less than 7/10 or artifact were excluded, as part of the fulfillment of the OSCAR-IB criteria [13]. Tracking software was utilized to ensure appropriate fixation. Average retinal OCT measures of both eyes were used in the analysis, and in case of monocular ON, only the non-ON eye was analyzed, given that it did not show evidence of subclinical ON.

### Cognitive testing

Cognitive function was evaluated through the following battery of cognitive tests administered by trained fellows at the MS center: The oral Symbol-Digit Modalities Test (SDMT), a speed of processing test widely used on MS patients [5], was administered in addition to the Montreal Cognitive Assessment–Arabic (MoCA) which is a cognitive impairment screening tool [10], and the Brief Visuospatial Memory Test–Revised (BVMT-R), extensively used in MS as well [14]. The SDMT score was determined by the number of correct answers in 90 s. MoCA score was given by the total score in the test (0–30). The BVMT-R test provided the total recall score, determined by the sum of recalled figures after trials 1, 2, and 3 (10 s each), and delayed recall (25 min).

### Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences software (IBM Corp. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). Statistical significance was defined as  $p < 0.05$ . The normality of distributions was evaluated through the Shapiro–Wilk test. Variables were classified as demographic and clinical (age, gender, disease duration, number of attacks, treatments, among others), physical disability (EDSS, 9-HPT, and T-25FWT), cognitive function (SDMT, MoCA, BVMT delayed recall, and total recall scores), and retinal OCT measures (pRNFL, GCIPL, and MV).

Associations between treatment groups were explored using the analysis of variance (ANOVA) and Bonferroni multiple comparisons test for physical disability, cognitive function, and OCT variables, and Chi-square ( $X^2$ ) test for

clinical and demographic variables. Bivariate correlations were explored (controlling for age, gender, disease duration, and level of education) for physical disability, cognitive function, and retinal OCT variables, reporting  $p$  values and Pearson and Spearman's rho correlation coefficients, which were consistent, but we report the latter, since it is more robust in our data, where the assumptions of constant variance and linearity were not met.

Linear regression analyses with Bonferroni adjustment for multiple comparisons were performed, reporting  $p$  values and Spearman correlation coefficients. Analyses of continuous variables with multivariable linear regression (adjusting for age, disease duration, MS treatment, and level of education) were performed using either pRNFL or GCIPL thickness in micrometers as the dependent variable, and the different cognitive function test scores as independent variables.

## Results

### Demographics and clinical characteristics

Forty-seven patients with RRMS and 18 healthy age- and gender-matched controls were recruited for the study. Of the 47 RRMS patients, 32 (68.1 %) were treated with interferon beta-1a and 15 (31.9 %) with fingolimod. There were no significant differences between treatment groups regarding age, disease duration, EDSS, T25FWT, 9HPT, cognitive tests scores, interval between first and second attack, number of the previous steroids courses, and vitamin D level. There mean EDSS and number of relapses until study visit was marginally higher in the fingolimod group (Table 1), reflecting the fact that it is currently used mainly as a second-line therapy. Furthermore, no significant differences were found between treatment groups regarding gender, history of ON, smoking status, and family history of MS, level of education, or semiology of the first attack (Table 1).

### OCT findings

One of the eyes of eight interferon and two fingolimod-treated patients were excluded from the analysis due to evidence of remote clinical or subclinical ON. The mean  $\pm$  SD pRNFL thickness in controls ( $99.5 \pm 8.9 \mu\text{m}$ ) was significantly greater than that in either interferon ( $92.9 \pm 8.7 \mu\text{m}$ )- or fingolimod ( $87.2 \pm 8.4 \mu\text{m}$ )-treated patients ( $p = 0.037$  and  $p < 0.0001$ , respectively) (Fig. 1). Similarly, the mean  $\pm$  SD GCIPL thickness was significantly higher in controls ( $86.8 \pm 4.2 \mu\text{m}$ ) than in Interferon ( $79.9 \pm 6.7 \mu\text{m}$ ,  $p = 0.001$ )- and Fingolimod ( $75.1 \pm 6.6 \mu\text{m}$ ,  $p < 0.0001$ )-treated patients (Table 1).

**Table 1** Clinical characteristics, cognitive scores, and retinal OCT measurements of the participants

Characteristic	Interferon	Fingolimod	Controls	<i>p</i> value
Number of subjects	32	15	18	–
Mean age (SD)	32.8 (11.2)	29.2 (9.4)	31.4 (7.8)	0.525 <sup>b</sup>
Females <i>N</i> (%)	18 (56.2)	8 (53.3)	8 (44.4)	0.722 <sup>a</sup>
Family history of MS (%)	12.5	20	NA	0.792 <sup>a</sup>
Current smoker (%)	46.8	33.4	NA	0.524 <sup>a</sup>
Education (%)			NA	0.328 <sup>a</sup>
High school	19.2	15.4		
University	80.8	69.2		
Master's	0	15.4		
MS duration in months (SD)	29.4 (24)	33.5 (24.1)	NA	0.592 <sup>c</sup>
History of optic neuritis (%)	15.6	13.4	NA	0.535 <sup>a</sup>
Mean interval between first two attacks in months (SD)	15.4 (17.2)	18.9 (10.7)	NA	0.581 <sup>c</sup>
Mean number of relapses until study visit (SD)	1.8 (1.1)	2.6 (1.5)	NA	0.052 <sup>b</sup>
Mean vitamin D level at study visit in ng/ml (SD)	54.2 (32.1)	55.9 (14.9)	NA	0.984 <sup>b</sup>
Mean EDSS (SD)	1 (1)	1.5 (1)	NA	0.111 <sup>c</sup>
Mean T25FWT in seconds (SD)	4.1 (1.1)	4.6 (2.2)	NA	0.353 <sup>c</sup>
Mean 9HPT in seconds (SD)	20.3 (3.1)	22.1 (4.1)	NA	0.091 <sup>b</sup>
Mean SDMT score (SD)	58.7 (13.1)	59.7 (17.5)	NA	0.831 <sup>b</sup>
Mean MoCA score (SD)	25.8 (2.7)	26.6 (2.6)	NA	0.339 <sup>b</sup>
Mean TR score (SD)	24.7 (7.8)	22.3 (10.3)	NA	0.401 <sup>b</sup>
Mean DR score (SD)	9.8 (3.1)	9.8 (2.8)	NA	0.949 <sup>b</sup>
Mean pRNFL in micrometers (SD)	92.9 (8.7)	87.2 (8.4)	99.5 (8.9)	0.001 <sup>b,*</sup>
Mean GCIPL in micrometers (SD)	79.9 (6.7)	75.1 (6.6)	86.8 (4.2)	<0.001 <sup>b,*</sup>
Mean MV in mm <sup>3</sup> (SD)	10 (0.5)	9.8 (0.5)	10.1 (0.3)	0.177 <sup>b</sup>

MS multiple sclerosis, EDSS expanded disability status scale, T25FWT timed 25-foot walk test, 9HPT 9-hole peg test, SDMT symbol-digit modality test, MoCA Montreal cognitive assessment tool, TR total recall score of the brief visuospatial memory test-revised (BVM-T-R), DR delayed recall score of the BVM-T-R, pRNFL peripapillary retinal nerve fiber layer, GCIPL ganglion cell/inner plexiform layer, MV macular volume

<sup>a</sup> Chi square ( $\chi^2$ ) test

<sup>b</sup> One-way analysis of variance (ANOVA)

<sup>c</sup> Mann–Whitney test

\*  $p < 0.05$

GCIPL thickness was significantly higher in interferon than fingolimod-treated patients ( $p = 0.036$ ) (Fig. 2). No significant differences in MV were found between groups, including healthy controls (Table 1).

### Bivariable correlations

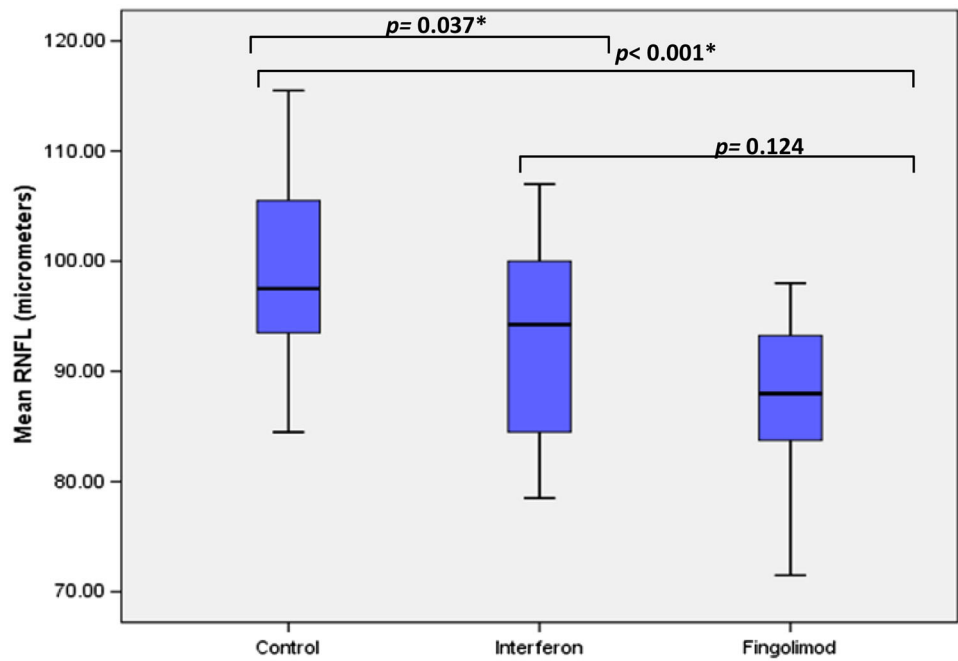
As expected, there was a negative correlation between age and SDMT score ( $r = -0.33$ ,  $p = 0.02$ ), as well as BVM-T total recall score ( $r = -0.35$ ,  $p = 0.02$ ), and a positive correlation between level of education and MoCA score ( $r = 0.42$ ,  $p = 0.01$ ). Cognitive scores given by the SDMT, total BVM-T recall, and delayed recall correlated negatively with physical disability variables EDSS, T25FWT, and 9HPT. There were no significant

correlations between disease duration and any of physical disability, cognitive, and retinal OCT variables.

### Multivariable analyses

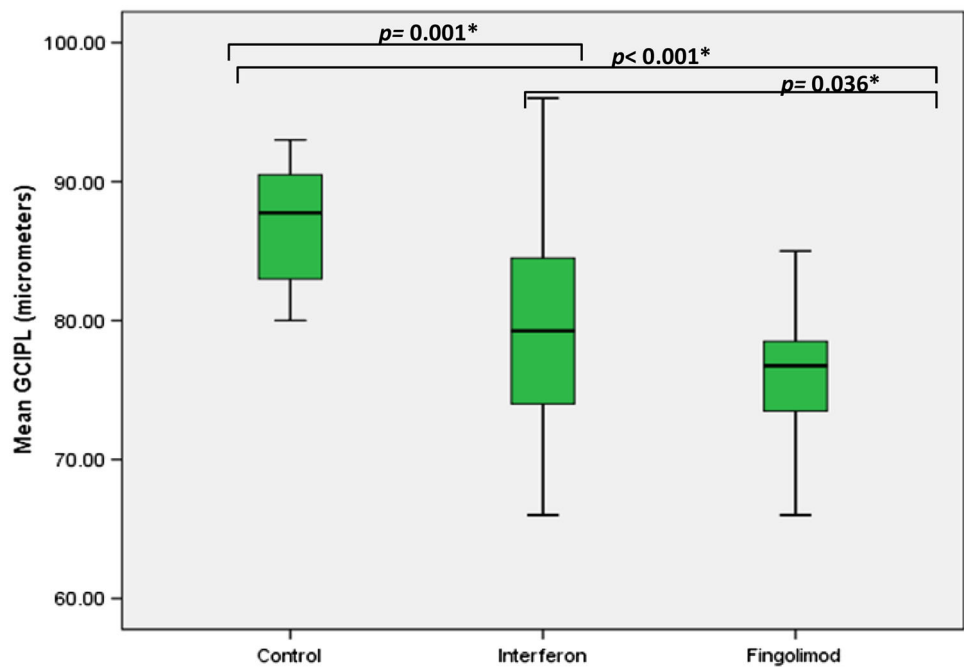
Multivariate analyses were performed controlling for age, disease duration, treatment group, and education when exploring cognitive tests, using Bonferroni adjusted alpha levels of 0.01 per test (0.05/5). EDSS correlated negatively with SDMT (standardized Beta  $-8.04$ ,  $p < 0.0001$ ), BVM-T total recall (standardized Beta  $-3.72$ ,  $p = 0.002$ ), and delayed recall scores (standardized Beta  $-1.49$ ,  $p < 0.0001$ ). Similarly, 9HPT correlated negatively with SDMT (standardized Beta  $-2.47$ ,  $p = 0.001$ ) but not the BVM-T delayed recall ( $p = 0.019$ ), total recall ( $p = 0.14$ ),

**Fig. 1** Mean peripapillary retinal nerve fiber layer (pRNFL). One-way analysis of variance (ANOVA). RNFL peripapillary retinal nerve fiber layer. \* $p < 0.05$



<sup>a</sup> One-way Analysis of Variance (ANOVA). RNFL= peripapillary retinal nerve fiber layer. \*  $p < 0.05$ .

**Fig. 2** Mean ganglion cell/inner plexiform layer (GCIPL). One-way analysis of variance (ANOVA). GCIPL ganglion cell/inner plexiform layer. \*  $p < 0.05$



<sup>a</sup> One-way Analysis of Variance (ANOVA). GCIPL= ganglion cell/inner plexiform layer. \*  $p < 0.05$ .

or MoCA ( $p = 0.26$ ). T25FWT correlated negatively with SDMT (standardized Beta  $-4.51$ ,  $p = 0.001$ ), BVMT total recall (standardized Beta  $-2.19$ ,  $p = 0.002$ ), and delayed recall scores (standardized Beta  $-0.42$ ,  $p = 0.01$ ), but not with MoCA ( $p = 0.095$ ) (Table 2).

There was a weak negative correlation between pRNFL thickness and EDSS (standardized Beta  $-0.13$ ,  $p = 0.01$ ) that became not significant when controlling for treatment group ( $p = 0.033$ ). However, pRNFL correlated negatively with the 9HPT (standardized Beta  $-0.2$ ,  $p < 0.0001$ ), but

**Table 2** Partial correlations between physical disability and cognitive scores

Variables	Standardized coefficients	<i>p</i> value
EDSS-SDMT	−0.54	<i>p</i> < 0.001*
EDSS-MoCA	−0.33	<i>p</i> = 0.04*
EDSS-TR	−0.47	<i>p</i> = 0.002*
EDSS-DR	−0.52	<i>p</i> = 0.001*
9HPT-SDMT	−0.49	<i>p</i> = 0.001*
9HPT-DR	−0.34	<i>p</i> = 0.03*
9HPT-MoCA	−0.12	<i>p</i> = 0.3
9HPT-TR	−0.13	<i>p</i> = 0.16
T25FWT-SDMT	−0.49	<i>p</i> = 0.002*
T25FWT-TR	−0.49	<i>p</i> = 0.003*
T25FWT-DR	−0.42	<i>p</i> = 0.01*
T25FWT-MoCA	−0.12	<i>p</i> = 0.12

Partial correlation coefficients adjusted for age, gender, disease duration, level of education, and treatment group

*SDMT* symbol-digit modality test, *TR* total recall score of the brief visuospatial memory test-revised (BVMT-R), *DR* delayed recall score of the BVMT-R, *MoCA* Montreal cognitive assessment tool, *9HPT* 9-hole peg test, *T25FWT* timed 25-foot walk test, *EDSS* expanded disability status scale

\* *p* < 0.05

not with the T25FWT (*p* = 0.57). Regarding cognitive function, pRNFL thickness correlated positively with the SDMT (standardized Beta 0.72, *p* = 0.007), but not with any of the MoCA, BVMT total recall, or delayed recall scores (*p* = 0.247, *p* = 0.168, and *p* = 0.132, respectively) (Fig. 3).

On the other hand, GCIPL thickness did not correlate with EDSS (*p* = 0.071), 9HPT (*p* = 0.03), or the T25FWT (*p* = 0.727). Furthermore, there were no significant correlations between MV and physical disability variables. As for cognitive function, GCIPL thickness did not correlate with any of SDMT (*p* = 0.411), MoCA (*p* = 0.91), BVMT total recall (*p* = 0.57), or delayed recall scores (*p* = 0.65). Similarly, MV did not correlate with any of SDMT (*p* = 0.39), MoCA (*p* = 0.63), BVMT total recall (*p* = 0.65), or delayed recall scores (*p* = 0.80) (Fig. 3).

## Discussion

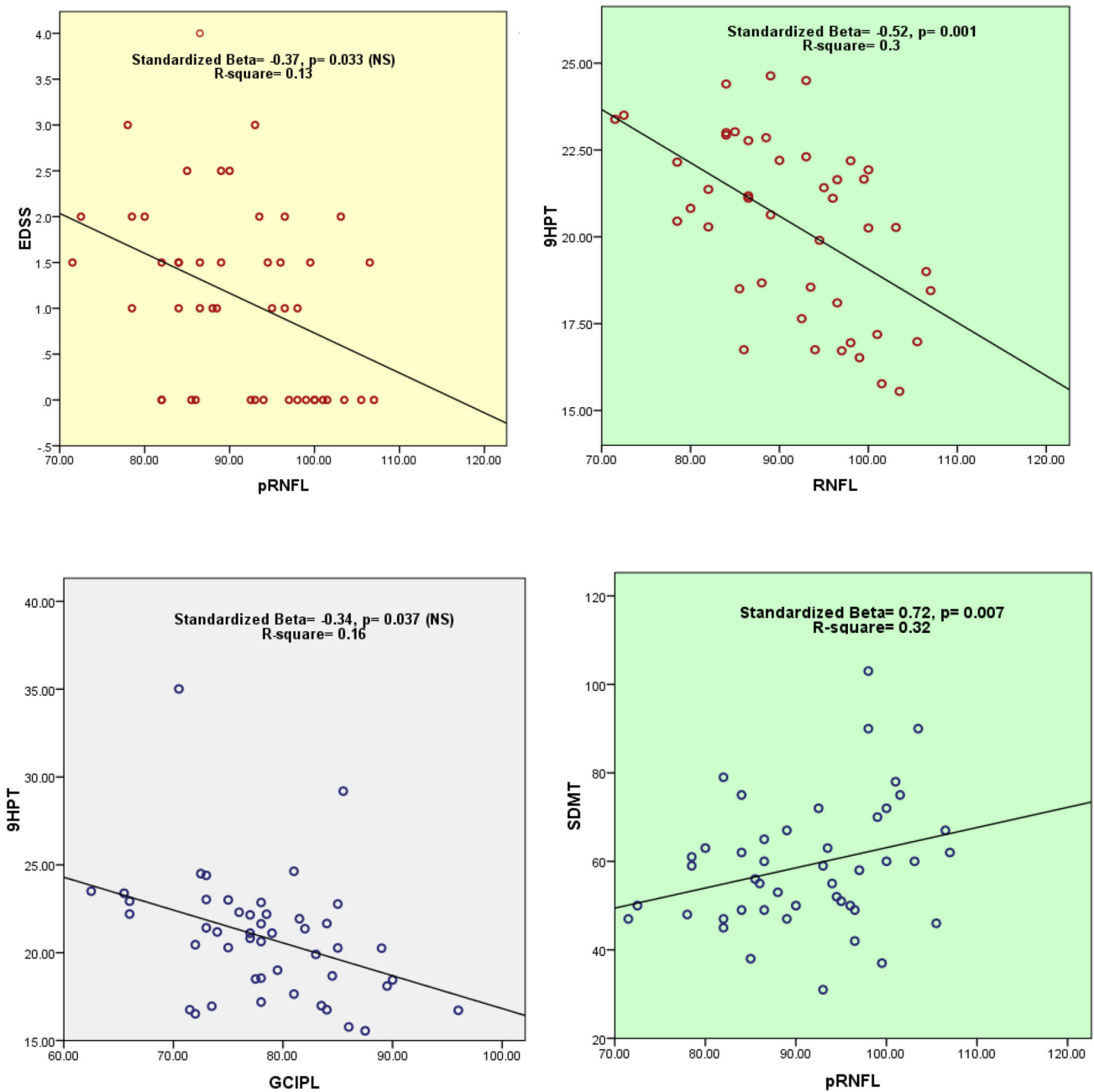
In this cohort of early MS patients (studying eyes without clinical or subclinical ON), there were no significant differences between fingolimod- or interferon-treated patients, regarding demographic and clinical characteristics, physical disability, and cognitive function scores. However, the mean pRNFL and GCIPL thickness in MS patients were significantly lower than that in controls. Such differences

are concordant with those described in the literature between controls and MS patients with longer disease duration and disability, as well as progressive forms of MS [15, 16]. Interestingly, GCIPL thickness was significantly higher in Interferon than in fingolimod-treated patients, perhaps, reflecting the current practice of using fingolimod as a second-line therapy. The negative correlation between age and SDMT as well as total recall score, and the positive correlation between level of education and MoCA score are expected as described in the literature [17], and highlight the importance of controlling for these variables when exploring any correlates for cognitive function scores, even in patients with the early MS.

The negative correlation between cognitive scores (SDMT, total recall, and delayed recall) and physical disability (EDSS, T25FWT, and 9HPT) indicates a linkage between the cognitive and physical disability domains early in the course of the disease. Such correlations have been described in other studies that included MS patients with longer disease duration and progressive MS [18, 19], although cognitive deterioration has been demonstrated in patients with early MS [5, 20]. Finding these correlations in early MS supports the inclusion of many of these scores (as the SDMT, T25FWT, and 9HPT) in the routine clinical follow-up parameters of MS patients, in addition to the EDSS.

Multivariable analyses controlling for age, disease duration, level of education, and treatment group, showed that pRNFL thickness correlated negatively with physical disability (9HPT), while it correlated positively with the SDMT, in spite of the extensive control of the covariates mentioned above and using Bonferroni adjustment for multiple testing. Similar correlations have been repeatedly described in literature, but in studies, including more advanced MS cohorts and progressive forms of MS [8, 11, 12, 21–25]. On the other hand, GCIPL thickness did not correlate with physical and cognitive disability in our cohort of patients. However, it has been shown in some studies that GCIPL changes occur in CIS patients and early MS, although many of the patients had subclinical ON [26]. In addition, GCIPL thickness has been shown in the literature to correlate well with MS subtype, active disease, and global brain pathology, but these studies included more disabled patients with longer disease duration as well [12, 17, 27]. It is possible that in this cohort of patients with early MS, the correlations between GCIPL thickness and physical/cognitive disability would become evident later in the course of the disease or when explored prospectively.

There has been extensive interest in OCT as a potential biomarker of axonal loss and neurodegeneration [28], and this is of paramount importance in MS due to the need to identify drugs with neuro-protective properties. The visual



**Fig. 3** Correlations between retinal measures and selected physical disability and cognitive scores. Multivariable linear regression models using Bonferroni adjusted alpha levels of 0.01 per test (controlling for age, disease duration, MS treatment, EDSS, and level of education for cognitive scores) using either pRNFL or GCIPL thickness in micrometers as the dependent variable, and the different cognitive

function test scores or physical disability scores as independent variables. *9HPT* 9-hole peg test, *EDSS* Kurtzke expanded disability status scale, *SDMT* symbol-digit modality test, *GCIPL* ganglion cell/inner plexiform layer, *pRNFL* peripapillary retinal nerve fiber layer, *NS* not statistically significant

pathway has been proposed as an excellent candidate to study neurodegeneration [23, 29] and is readily accessible for testing with non-invasive techniques. This has been even more persuading after improvement in the OCT technology, gaining the ability to segment all the retinal layers, and after evidence of retinal changes in MS in the absence of ON [21, 30]. Recent prospective OCT studies on patients with

relapsing and progressive forms of MS and heterogeneous disease duration showed that retinal changes occur mostly over the first years, emphasizing the importance of early intervention [31]. Our study confirms the correlations between retinal OCT measures and physical and cognitive function, in non-ON eyes of the early RRMS patients, supporting its use early in the course of the disease.

Among the limitations of this study is the lack of inclusion of MS patients on other therapies, which would have allowed generalizing the conclusions to the rest of the MS patients. However, we needed to restrict our sample to patients with disease duration of 5 years or less. Moreover, baseline characteristics as disease duration and number of relapses are imbalanced between treatment groups due to our practice of using fingolimod as second-line therapy. A prospective study design would enable us to explore how cognitive function, physical disability, and retinal OCT measures change over time in this group of patients with the early MS. Furthermore, exploring other retinal layers, such as the macular RNFL (mRNFL) and nuclear layers, would have been interesting to determine any added value for monitoring these measures in the early MS.

## Conclusion

In patients with early MS, without clinical or subclinical optic neuropathy, there is an association between cognitive and physical disability domains early in the course of the disease. Furthermore, retinal thickness measures correlated with physical and cognitive disability, supporting their potential use as biomarkers of axonal loss and neurodegeneration.

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## Compliance with ethical standards

**Conflicts of interest** On behalf of all authors and contributors, this is to acknowledge that there is no conflict of interest.

**Ethical standard** This study have been approved by the appropriate ethics committee and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

**Informed consent** All persons gave their informed consent prior to their inclusion in the study.

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