

Cognitive impairment in patients with multiple sclerosis is associated with atrophy of the inner retinal layers

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Abstract

Background: Inner retinal layer (IRL) atrophy is a potential biomarker for neurodegeneration in multiple sclerosis (MS).

Objective: To investigate the relationship between cognitive impairment and IRL atrophy in MS.

Methods: Cross-sectional study design, including 217 patients and 59 healthy controls. Subjects were investigated clinically, underwent retinal optical coherence tomography (OCT) and comprehensive cognitive assessments. The association between these modalities was evaluated by regression analyses.

Results: Of the patients, 44.2% were cognitively impaired. In the absence of multiple sclerosis-associated optic neuritis (MSON), cognitively impaired patients had a significantly lower mean peripapillary retinal nerve fiber layer (pRNFL, Δ : 8.13 μm , $p < 0.001$) and mean macular ganglion cell–inner plexiform layer (mGCIPL, Δ : 11.50 μm , $p < 0.001$) thickness compared to cognitively preserved patients. There was a significant association between the presence of cognitive impairment and pRNFL (odds ratio (OR): 1.11, 95% confidence interval (CI): 1.04–1.18, $p = 0.001$) and mGCIPL (OR = 1.11, 95% CI = 1.05–1.18, $p < 0.001$) atrophy. This association was masked by the severe IRL atrophy seen following MSON.

Conclusion: The strong relationship between cognitive impairment across multiple cognitive domains and atrophy of the pRNFL and mGCIPL in patients who never suffered from MSON suggests that OCT is useful in assessing central nervous system neurodegeneration in MS.

Keywords: Multiple sclerosis, retinal optical coherence tomography, cognitive impairment, retinal nerve fiber layer, ganglion cell–inner plexiform layer, inner retinal layer atrophy

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Introduction

Cognitive dysfunction and multiple sclerosis-associated optic neuritis (MSON) have long been recognized as relevant to a patient's disability in multiple sclerosis (MS).¹ Cognitive impairment is present in 40%–70% of patients and contributes to a significant decrease in quality of life.^{1–3} Frequently observed problems include deficits in information processing speed, long-term memory, and executive functioning.^{1,4} Brain imaging studies have demonstrated that cognitive impairment in MS is related to brain atrophy, an important sign of neurodegeneration.^{2,4–6}

The anterior visual system offers a suitable model to study MS-related disease mechanisms.⁷ Importantly, the association of MSON with retinal optical

coherence tomography (OCT) has been exhaustively investigated and is now well established.^{8,9} In recent years, retinal OCT has also been used as a sensitive and more practical alternative to magnetic resonance imaging (MRI) for the analysis of the process of neurodegeneration in MS.^{8,10} The relationship between cognitive impairment and inner retinal layer (IRL) atrophy, however, is less well known. One single study found a possible link between cognitive impairment and peripapillary retinal nerve fiber layer (pRNFL) atrophy¹¹ but definitive results are lacking. Moreover, advancements in OCT technology and software have led to more reliable segmentation of individual macular layers, most importantly the macular ganglion cell–inner plexiform layer (mGCIPL).

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Therefore, the aim of this study was to test whether MS disease-related atrophy of the pRNFL and mGCIPL, measured with spectral domain OCT, is associated with cognitive impairment as assessed across several cognitive domains using a battery of validated psychometric tests in a large cohort of patients with MS.

Methods

Study population

In this observational, cross-sectional study, patients were included from the Amsterdam MS Cohort at the VU University Medical Centre Amsterdam. This cohort has been described previously.¹² In brief, all patients included in this study had a diagnosis of relapsing remitting (RR), secondary progressive (SP), or primary progressive (PP) MS¹³ and were required to be between 18 and 80 years of age at time of inclusion. Exclusion criteria were a relapse or corticosteroid treatment 1 month prior to inclusion, pregnancy, any other previous neurological or neuropsychiatric disorders, a history of alcohol or drug abuse, or central nervous system (CNS) comorbidity showing on MRI which could not be attributed to MS. The same exclusion criteria applied to the healthy control (HC) group which consisted of subjects who had to be between 40 and 60 years of age, without any neurological or psychiatric disease and who were not related (within the first or second degree of consanguinity) to a patient with MS. All subjects with high refractive errors (> -6.0 or $+6.0$ dpt.) or ocular diseases affecting the retina were excluded.

This study was approved by the medical ethics committee (protocol number 2010/336) and the scientific research committee (protocol number CWO/10-25D) of the VU University Medical Centre. Written informed consent was obtained from all participants.

OCT imaging

OCT imaging was performed by four trained technicians on a spectral domain OCT (software version 1.7.1.0.; Spectralis, Heidelberg Engineering, Heidelberg, Germany), with dual beam simultaneous imaging and the eye-tracking function enabled for optimal measurement accuracy.¹⁴ Room-lighting conditions were dimmed and no pharmacological pupil dilation was used. A 12° peripapillary ring scan (1536 A-scans, 1 B-scan, no predetermined automatic real time (ART)) manually centered around the optic nerve head and a 20° × 20° macular volume scan (512 A-scans, 49 B-scans, vertical alignment, ART 16) manually centered around the fovea were performed.

Individual retinal layer thicknesses were obtained by automated segmentation software provided by the manufacturer (HRA/Spectralis Viewing Module version 5.6.4.0). Quality control (QC) was performed according to validated international consensus QC criteria (OSCAR-IB)¹⁵ by two co-authors (L.J.B. and A.P.) who were blind to the results of the neuropsychological examination. On QC, a small proportion of scans were identified with algorithm failures which could readily be manually corrected. Scans where algorithm failures were not due to automated image post-processing, but violation of other OSCAR-IB criteria, were excluded from further analyses.

For pRNFL thickness, the global mean of the entire pRNFL was used. For the macular scan, the software provides a thickness map for every retinal layer on a 1-, 3-, and 6-mm grid (as is defined by the Early Treatment Diabetic Retinopathy Study¹⁶). Because of the low contrast between the ganglion cell layer and the inner plexiform layer, these two layers were combined to form the mGCIPL.¹⁰ For the mGCIPL, the mean thickness of the inner four quadrants of the grid (corresponding to the 3-mm ring, excluding the 1-mm center ring) was used.

Cognitive and clinical assessment

All subjects received an extensive neuropsychological examination consisting of Rao's Brief Repeatable Battery of Neuropsychological Tests (BRB-N) and three additional cognitive tests, which have been described previously.¹⁷ Each test corresponds to a different cognitive domain. The examination was administered by three trained research assistants according to a standardized protocol, who were blind to the results of the OCT. The BRB-N consists of the Selective Reminding Test (SRT, measuring verbal memory), Symbol Digit Modalities Test (SDMT, measuring information processing speed), Word List Generation Test (measuring verbal fluency), and 10/36 Spatial Recall Test (10/36 SPRT, measuring visuospatial memory).¹⁸ The Paced Auditory Serial Addition Test was excluded due to multiple disadvantages.¹⁹ The three additional test comprised the Concept Shifting Test (CST, measuring executive functioning), Stroop Color Word test (measuring attention), and Memory Comparison Test (MCT, measuring working memory). The raw test scores were corrected for the effects of age, sex, and level of education using a linear regression model in the same way as Amato *et al.*,²⁰ correcting only for those factors that had a significant effect on the test score. Z-scores were calculated for each individual domain. Consistent with previous publication from our center,

a patient was considered cognitively impaired if he or she scored at least 1.5 standard deviation (SD; $Z \leq 1.5$) below the average of the HCs on two or more domains.¹⁷

A history of MSON was determined per consensus protocol.²¹ The degree of physical disability was assessed by trained and certified physicians using the Expanded Disability Status Scale (EDSS). All examinations, including OCT, were performed on the same day.

Statistical analysis

Because of the large effect MSON has on IRL thickness,⁹ patients were grouped accordingly. The binocular average pRNFL and mGCIPL thickness was calculated for each subject. This approach was mandatory because the outcome measure, which is the presence or absence of cognitive impairment, was measured on patient level and not eye level. This approach is also in accordance with reporting guidelines, which specifically mention exceptions to frequently used models for adjustment of inter-eye correlations, such as generalized estimating equations.¹⁰ In order to avoid the introduction of noise by pooling MSON eyes and MSNON eyes (eyes without a history of MSON) within the same patient, only patients with the same history of MSON in both eyes (so bilateral MSON and bilateral MSNON) were analyzed. At no point were data from MSON and MSNON eyes combined as a mean. Results for the MSON and MSNON group are shown separately.

Normal data distribution was assessed graphically. Differences in demographic variables between patients and HCs and between cognitively impaired and cognitively preserved patients were analyzed using chi-square test for categorical variables, two-tailed *t*-test for parametric continuous variables and Mann–Whitney U test for non-parametric continuous variables. Differences in IRL thickness between the aforementioned groups were tested using multiple linear regression analyses with cognitive status (HC, cognitively preserved, and cognitively impaired) as a categorical variable, adjusting for age and sex.

In order to investigate whether IRL atrophy is associated with the presence of cognitive impairment, we performed binary logistic regression analyses, with adjustment for age and sex. Two models were used, one with IRL thickness as a continuous variable and one with IRL thickness as a categorical variable by dichotomizing the subjects according to median

thickness. In the MSNON group, this resulted in a group with pRNFL thickness $\leq 85.0 \mu\text{m}$ and pRNFL thickness $>85.0 \mu\text{m}$. Likewise, patients were divided in a group with mGCIPL thickness $\leq 88.1 \mu\text{m}$ and mGCIPL thickness $>88.1 \mu\text{m}$. In the MSON group, patients were dichotomized in a group with pRNFL thickness $\leq 75.0 \mu\text{m}$ and pRNFL thickness $>75.0 \mu\text{m}$, and mGCIPL thickness $\leq 73.0 \mu\text{m}$ and mGCIPL thickness $>73.0 \mu\text{m}$. Correlations between IRL thickness and scores on cognitive subtests were analyzed using partial correlation coefficients (*r*), adjusting for age and sex. All analyses were performed using SPSS version 22.0. Statistical significance was set at $p < 0.05$.

Results

The Amsterdam MS Cohort consists of a total of 230 MS patients and 63 HC subjects. Five patients were excluded due to uncertain diagnosis or suspected alcohol and/or drug abuse. Eight patients and four HCs were excluded due to insufficient data on the neuropsychological examination. The presented results concern the remaining 217 MS patients and 59 HCs. Following QC, 193/1104 (17.5%) of the OCT scans were rejected.

Characteristics of the patients and HC subjects

Table 1 shows the characteristics of the patients (all patients as well as the two clinical subgroups) and the 59 HCs. Compared to HCs, patients were older (mean difference = 3.91 years, $p = 0.001$) and were slightly more likely to be female, though the latter was statistically not significant. Patients had a mean disease duration of over 20 years and a median EDSS score of 4.0 (range = 1.0–8.0). Most patients had a RR course (61.3%), followed by a SP (25.8%) and a PP (12.9%) course. Overall, patients showed significant thinning of both the pRNFL and the mGCIPL compared to HCs (mean difference = $8.51 \mu\text{m}$, $p < 0.001$ and $11.55 \mu\text{m}$, $p < 0.001$), with MSON patients showing more atrophy than MSNON patients (Table 1).

In total, 44.2% (96/217) of the patients were classified as cognitively impaired, compared to 6.8% (4/59) of the HCs ($p < 0.001$). Cognitively impaired patients were older (mean difference = 3.99 years, $p = 0.003$) and had a longer disease duration (mean difference = 2.50 years, $p = 0.011$). In addition, cognitively impaired patients had a higher median EDSS score (4.5 vs 3.0, $p < 0.001$; Supplementary Table 1).

Subsequently, patients were stratified according to MSON history resulting in 102 (47.0%) bilateral

Table 1. Characteristics of patients with multiple sclerosis and healthy control subjects.

	All patients, N=217	MSNON patients, N=102	MSON patients, N=35	Healthy controls, N=59	p-value	
					Patients vs HCs	MSNON vs MSON
Age (years), mean±SD	54.30±9.96	55.91±10.00	53.18±9.75	50.39±7.28	0.001	0.133
Sex (male:female)	67:150	37:65	11:24	22:37	0.350	0.604
Disease duration (years), mean±SD	20.34±6.99	19.34±7.05	22.78±7.34	N/A	N/A	0.015
EDSS, median (range)	4.0 (1.0–8.0)	3.75 (1.0–7.5)	4.0 (1.5–7.5)	N/A	N/A	0.813
Type of MS						
RR	133 (61.3%)	56 (54.9%)	22 (62.9%)	N/A	N/A	0.043
SP	56 (25.8%)	21 (20.6%)	11 (31.4%)			
PP	28 (12.9%)	25 (24.5%)	2 (5.7%)			
Use of disease modifying therapy						
Current	61 (28.1%)	24 (23.5%)	10 (28.6%)	N/A	N/A	< 0.001
Past	40 (18.4%)	9 (8.8%)	12 (34.3%)			
Never	116 (53.5%)	69 (67.6%)	13 (37.1%)			
Cognitive impairment (CP:CI)	121:96	61:41	20:15	55:4	<0.001	0.782
pRNFL thickness (µm), mean±SD	83.16±11.18	85.62±10.29	75.04±10.33	91.67±6.82	<0.001	<0.001
mGCIPL thickness (µm), mean±SD	82.66±14.89	86.12±12.29	69.86±16.88	94.21±6.08	<0.001	<0.001

MSNON: no history of multiple sclerosis-associated optic neuritis; MSON: multiple sclerosis-associated optic neuritis; HC: healthy control; EDSS: Expanded Disability Status Scale; RR: relapsing remitting; SP: secondary progressive; PP: primary progressive; CP: cognitively preserved; CI: cognitively impaired; pRNFL=peripapillary retinal nerve fiber layer; mGCIPL: macular ganglion cell-internal plexiform layer.
The mean±SD, median (range), and frequency (%) are presented. Data are presented for all patients, as well as for the two clinical subgroups (MSNON and MSON) and the HCs.

MSNON patients and 35 (16.1%) bilateral MSON patients. In total, 61 (28.1%) patients had a history of unilateral MSON, and in 19 (8.8%) patients, the history of MSON was unclear.

IRL thickness in MSNON and MSON patients

MSNON patients. Table 2 shows the characteristics of the MSNON group in which 41 patients (40.2%) were classified as cognitively impaired and 61 (59.8%) as cognitively preserved. There was no significant difference in mean age or mean disease duration between the two groups. Cognitively impaired patients did, however, show a higher degree of disability (median EDSS score=4.5 vs 3.0, $p<0.001$) and were more likely to suffer from a progressive form of the disease. Patients scored the worst on the SDMT and MCT (for more details, see Supplementary Table 2).

Cognitively impaired MSNON patients showed a large and statistically significant degree of atrophy compared to cognitively preserved patients for both the pRNFL and the mGCIPL (mean difference=8.13 µm, $p<0.001$; 11.50 µm, $p<0.001$; Table 2 and Figure 1). Cognitively preserved patients showed a small difference in pRNFL and mGCIPL thickness

compared to HCs, but this was statistically not significant (mean difference=2.95 µm, $p=0.098$; 3.58 µm, $p=0.119$).

MSON patients. In the MSON group, 15/35 patients (42.9%) were classified as cognitively impaired. Cognitively preserved MSON patients showed substantial atrophy of both the pRNFL and the mGCIPL compared to HCs (mean difference=15.29 µm, $p<0.001$; 24.42 µm, $p<0.001$), but there were no differences in either pRNFL or mGCIPL thickness between the cognitively impaired and cognitively preserved MSON patients (mean difference=4.38 µm, $p=0.159$; -0.23 µm, $p=0.879$; Figure 1. For detailed demographic data and cognitive test results of this subgroup, see Table 3 and Supplementary Table 2.

Association between IRL thickness and cognitive impairment

MSNON patients. pRNFL thickness showed a significant, inverse association with cognitive impairment with an odds ratio (OR) of 1.09 (95% CI=1.03–1.15, $p=0.002$) indicating that thinning of the pRNFL by 1 µm increases the odds of being cognitively impaired by 1.09. Likewise, the mGCIPL showed a similar significant association with cognitive impairment, with

Table 2. Characteristics of the MSNON patients: Characteristics of the cohort of patients with MS who never experienced an episode of MS-associated optic neuritis dichotomized into those who were cognitively impaired and those who were cognitively preserved.

	Cognitively impaired, N=41	Cognitively preserved, N=61	p-value
Age (years), mean ± SD	57.66 ± 9.59	54.73 ± 10.17	0.149
Sex (male:female)	19:22	18:43	0.083
Disease duration (years), mean ± SD	20.55 ± 7.97	18.52 ± 6.29	0.154
EDSS, median (range)	4.5 (3.5–6.5)	3.0 (2.5–5.0)	<0.001
Type of MS			0.029
RR	16 (39.0%)	40 (65.6%)	
SP	12 (29.3%)	9 (14.8%)	
PP	13 (31.7%)	12 (19.7%)	
Use of disease modifying therapy			0.515
Current	10 (24.4%)	14 (23.0%)	
Past	2 (4.9%)	7 (11.5%)	
Never	29 (70.7%)	40 (65.6%)	
pRNFL thickness (µm), mean ± SD	80.59 ± 8.49	88.72 ± 10.14	<0.001
mGCIPL thickness (µm), mean ± SD	79.13 ± 13.53	90.63 ± 9.02	<0.001

EDSS: Expanded Disability Status Scale; RR: relapsing remitting; SP: secondary progressive; PP: primary progressive; pRNFL: peripapillary retinal nerve fiber layer; mGCIPL: macular ganglion cell–inner plexiform layer.
The mean ± SD, median (range), and frequency (%) are presented.

an OR of 1.10 (95% CI=1.04–1.16, $p<0.001$). Both associations remained significant after adjusting for age and sex, resulting in an OR for pRNFL of 1.11 (95% CI=1.04–1.18, $p=0.001$) and an OR for mGCIPL of 1.11 (95% CI=1.05–1.18, $p<0.001$; Figure 2(a)).

In order to further investigate the effect of severe IRL atrophy, we dichotomized the patients according to IRL thickness. Patients with pRNFL thickness equal to or less than 85.0 µm had a significantly increased odds of being cognitively impaired compared to patients with pRNFL thickness >85.0 µm, OR=4.63 (95% CI=1.69–12.70, $p=0.003$). Similarly, patients with an mGCIPL thickness equal to or below 88.1 µm had a significantly increased odds of being cognitively impaired (OR=3.66, 95% CI=1.36–9.86, $p=0.010$) compared to patients with an mGCIPL thickness above 88.1 µm. Again, the results remained significant after adjusting for age and sex with an OR of 5.42 (95% CI=1.78–16.53, $p=0.003$) for the pRNFL and an OR of 3.83 (95% CI=1.38–10.68, $p=0.010$) for the mGCIPL (Figure 2(b)). Adjusting the data for the use of disease-modifying treatment (never, past, current use) did not have any effect on the observed effect. pRNFL thickness was only significantly correlated with the SDMT ($r=0.34$, $p=0.004$) and MCT score ($r=0.24$, $p=0.042$), whereas mGCIPL thickness correlated with every test score and most strongly with the CST ($r=0.46$, $p<0.001$) and 10/36 SPRT ($r=0.42$, $p<0.001$; Table 4).

MSNON patients. In the MSNON group, there was no significant association between pRNFL (OR=1.04, 95% CI=0.96–1.14, $p=0.350$) nor mGCIPL (OR=1.00, 95% CI=0.94–1.06, $p=0.978$) thickness and cognitive impairment. After adjusting for age and sex this did not change (pRNFL: OR=1.10, 95% CI=0.97–1.25, $p=0.122$; mGCIPL: OR=1.04, 95% CI=0.95–1.13, $p=0.399$; Figure 2(a)). Patients with a pRNFL thickness equal to or less than 75.0 µm had an increased odds of being cognitively impaired, but this was statistically not significant (unadjusted OR=4.17, 95% CI=0.61–28.62, $p=0.147$; adjusted OR=59.99, 95% CI=0.60–6035.07, $p=0.082$). There was no association between the dichotomized mGCIPL thickness and cognitive impairment (unadjusted OR=1.00, 95% CI=0.15–6.77, $p=1.00$; adjusted OR=0.73, 95% CI=0.066–8.17, $p=0.801$; Figure 2(b)). Again, adjusting for use of disease-modifying treatment did not alter the results. There were no significant correlations between test scores and IRL thickness, apart from a correlation between pRNFL thickness and the SRT score ($r=0.58$, $p=0.007$; Table 4).

Discussion

This study provides strong evidence for a relationship between atrophy of the pRNFL and mGCIPL and cognitive impairment in patients with MS. The results demonstrate that cognitively impaired MSNON patients show substantial and highly significant thinning of both the pRNFL and the mGCIPL compared

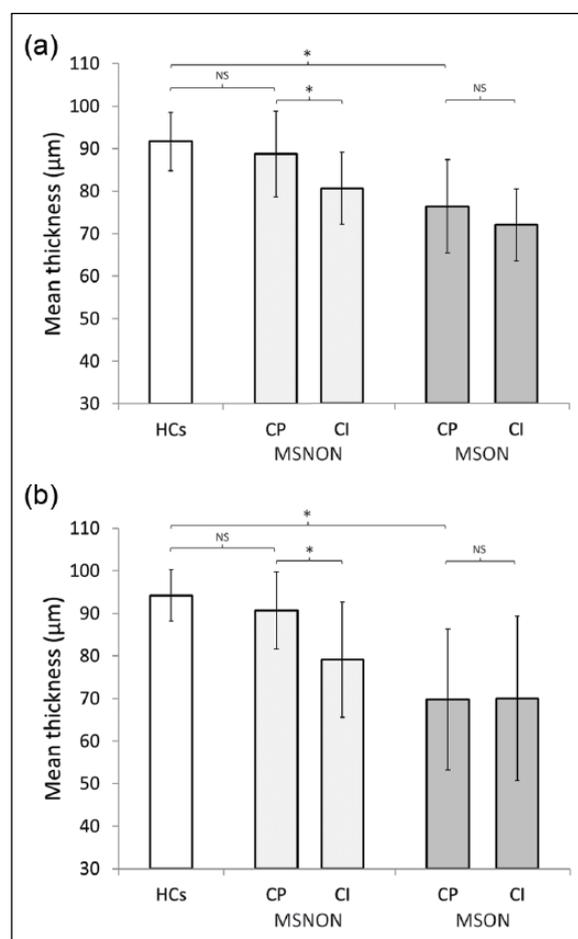


Figure 1. Mean pRNFL and mGCIPL thickness in HCs, MSNON patient, and MSON patients. Patients are dichotomized according to cognitive status. Data are presented for (a) pRNFL and (b) mGCIPL. Error bars represent standard deviations. Differences in retinal layer thickness were tested using multiple linear regression analyses, adjusting for age and sex. $*p < 0.001$. pRNFL: peripapillary retinal nerve fiber layer; mGCIPL: macular ganglion cell–inner plexiform layer; HC: healthy control; CP: cognitively preserved; CI: cognitively impaired; MSNON: no history of multiple sclerosis–associated optic neuritis; MSON: multiple sclerosis–associated optic neuritis; NS: not significant.

to cognitively preserved MSNON patients. More importantly, in this same patient group, atrophy of the pRNFL and mGCIPL was significantly associated with an increased odds of being cognitively impaired, taking other disease-related factors into account. As expected, a history of MSON caused severe IRL atrophy which masked any relationship to cognitive function. This masking effect of MSON has been described before.²² The extremely high OR for the adjusted, dichotomized pRNFL is caused by the small number of patients.

Our findings confirm and extend on the time-domain OCT data by Toledo *et al.*¹¹ in which the authors

found a trend toward a lower average pRNFL thickness in cognitively impaired MS patients. They also found significant correlations between the average and temporal pRNFL thickness and test scores on some subtests of Rao's BRB-N, particularly the SDMT. In contrast, three other studies failed to demonstrate a relationship between pRNFL thickness and test scores on various neuropsychological tests.^{23–25} There are important differences between these studies and our study with regard to the study populations, which were of shorter disease duration, and the pooling of data from MSNON and MSON eyes.

There have been no previous studies on the relationship between cognitive impairment and mGCIPL thickness, but the association found is anatomically logical. The retinal ganglion cell residing in the mGCIPL and the axon residing in the RNFL form one anatomical unit. The first to third order neurons of the optic pathways are known to intimately share their fate through retrograde axonal degeneration.^{26,27} The finding that in the absence of MSON, the main contributor to retrograde axonal degeneration, atrophy of the IRL was strongly associated with cognitive impairment implies that a more systemic degree of neurodegeneration is at play. This interpretation extends on the anatomically restrictive definition of axonal degeneration in the visual system alone. This argument is strengthened by studies showing a relationship with physical disability measured by EDSS and disease course.^{28–32}

One limitation of this study is its cross-sectional design; we are therefore in the process of re-investigating all patients after a 4-year interval. Another limitation is the long disease duration which could introduce a potential bias toward patients with more severe neurodegeneration affecting cognitive function.¹ Likewise, the potential of a “plateau effect” of IRL atrophy in the later disease course needs to be considered.³³ The latter two concerns underline the importance for longitudinal studies in patients with early disease. Because of the deleterious effect of MSON, such studies should focus on patients with clinically isolated syndromes other than MSON. With respect to the neuropsychological examination, there is a lack in agreement regarding the criteria of cognitive impairment in MS patients. For internal consistency, we have therefore strictly adhered to the multi-cognitive domain 1.5 SD criterion consistently used in previous publications from our center. We note the difference in age between patients and HCs but we corrected this by adjusting all analyses for age (among others). Another limitation is the fact that the assessment of MSON was merely based on clinically confirmed episodes and patient-reported history.

Table 3. Characteristics of the MSON patients: Characteristics of the cohort of patients with bilateral MS-associated optic neuritis dichotomized into those who were cognitively impaired and those who were cognitively preserved.

	Cognitively impaired, N=15	Cognitively preserved, N=20	p-value
Age (years), mean±SD	55.97±10.27	51.10±9.05	0.146
Sex (male:female)	5:10	6:14	0.833
Disease duration (years), mean±SD	24.40±7.64	21.56±7.06	0.263
EDSS, median (range)	4.5 (4.0–6.0)	3.0 (2.5–4.5)	0.008
Type of MS			0.112
RR	7 (46.6%)	15 (75.0%)	
SP	6 (40.0%)	5 (25.0%)	
PP	2 (13.3%)	0 (0.0%)	
Use of disease modifying therapy			0.853
Current	5 (33.3%)	5 (25.0%)	
Past	5 (33.3%)	7 (35.0%)	
Never	5 (33.3%)	8 (40.0%)	
pRNFL thickness (µm), mean±SD	72.00±8.46	76.38±11.03	0.159
mGCIPL thickness (µm), mean±SD	70.02±19.27	69.79±16.54	0.879

EDSS: Expanded Disability Status Scale; RR: relapsing remitting; SP: secondary progressive; PP: primary progressive; pRNFL: peripapillary retinal nerve fiber layer; mGCIPL: macular ganglion cell–inner plexiform layer. The mean±SD, median (range), and frequency (%) are presented.

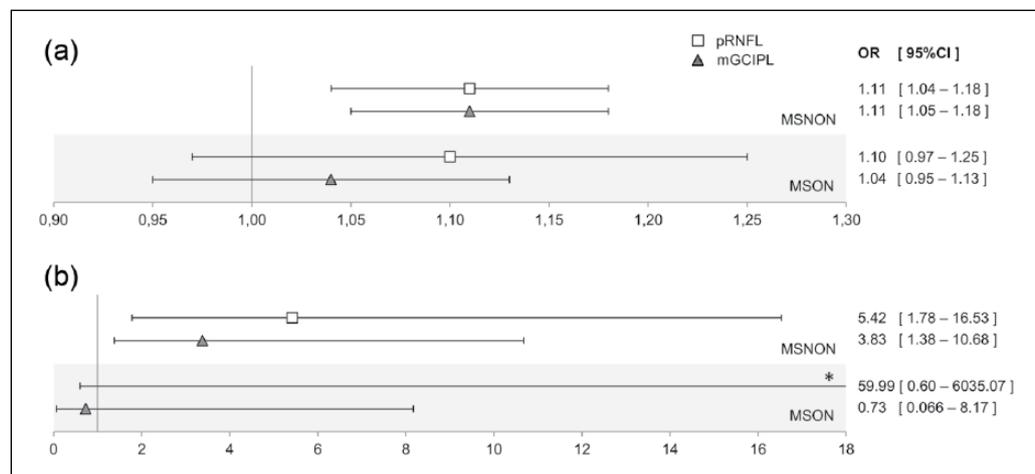


Figure 2. Adjusted odds ratios for pRNFL and mGCIPL to determine cognitive impairment in patients with MS. Data are presented for clinical subgroups (MSNON and MSON). The OR and 95% CI were significant and comparable in effect size when data were analyzed both on a rational scale (a: continuous data) and categorical scale (b: dichotomized data).

*OR and 95% CI exceed graph axis limits.

pRNFL: peripapillary retinal nerve fiber layer; mGCIPL: macular ganglion cell–inner plexiform layer; MSNON: no history of multiple sclerosis-associated optic neuritis; MSON: multiple sclerosis-associated optic neuritis; OR: odds ratio; 95% CI: 95% confidence interval.

Although this approach is consistent with other studies in the field, subclinical episodes may have gone unnoticed.

The strength of this study is its large sample size which, among others, made it possible to conduct the research in patients with bilateral MSNON eyes. Previous OCT studies often included the unaffected contralateral eyes of unilateral MSON patients as

well. We chose to exclude patients with a history of a unilateral episode of MSON, and thus limiting our sample size, because the contralateral unaffected eyes of MSON eyes are known to show more atrophy than bilateral MSNON eyes.⁹

In summary, in this paper, we provide for the first time evidence for a strong relationship between atrophy of the pRNFL and mGCIPL and cognitive

Table 4. Partial correlation coefficients (*r*) between pRNFL and mGCIPL thickness and test scores of separate cognitive tests.

	MSNON		MSON		MSON		MSON	
	pRNFL (<i>r</i>)	<i>p</i> -value	mGCIPL (<i>r</i>)	<i>p</i> -value	pRNFL (<i>r</i>)	<i>p</i> -value	mGCIPL (<i>r</i>)	<i>p</i> -value
SRT	0.21	0.075	0.32	0.007	0.580	0.007	0.35	0.174
SDMT	0.34	0.004	0.29	0.014	0.26	0.225	0.20	0.433
WLGT	0.21	0.079	0.24	0.039	0.013	0.954	-0.068	0.789
10/36 SPRT	0.18	0.137	0.42	< 0.001	0.256	0.262	0.20	0.422
CST	0.22	0.062	0.46	< 0.001	0.211	0.358	0.30	0.221
SCWT	0.12	0.304	0.25	0.037	0.16	0.493	0.24	0.354
MCT	0.24	0.042	0.26	0.032	0.011	0.962	0.27	0.282

MSNON: no history of multiple sclerosis-associated optic neuritis; MSON: multiple sclerosis-associated optic neuritis; pRNFL: peripapillary retinal nerve fiber layer; mGCIPL: macular ganglion cell-inner plexiform layer; SRT: Selective Reminding Test; SDMT: Symbol Digit Modalities Test; WLGT: Word List Generation Test; 10/36 SPRT: 10/36 Spatial Recall Test; CST: Concept Shifting Test; SCWT: Stroop Color Word Test; MCT: Memory Comparison Test.

impairment in patients with MS, suggesting that retinal OCT might be useful in assessing systemic neurodegeneration in MS.

Declaration of Conflicting Interests

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