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Retinal nerve fiber layer thickness associates with cognitive impairment and physical disability in multiple sclerosis

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ABSTRACT

Background: Reductions of the peripapillary retinal nerve fiber layer (pRNFL) thickness has been indicated even in early-stages of multiple sclerosis (MS). The aim was to investigate the association between pRNFL thickness, measured with optical coherence tomography (OCT), and physical disability and cognitive impairment in MS.
Methods: 465 MS patients and 168 healthy controls (HCs) were included. MS subjects were divided into subgroups according to disease subtype. All subjects underwent OCT examination of all pRNFL quadrants using Canon OCT-HS100. Associations were tested using linear mixed effect models. Physical disability was assessed with the Expanded Disability Status Scale (EDSS) and cognitive function with the Symbol Digit Modalities Test (SDMT).
Results: The average pRNFL, inferior pRNFL and temporal pRNFL thicknesses were significantly correlated to both EDSS ($-1.0\,\mu m$, $p < 0.01$; $-1.2\,\mu m$, $p < 0.05$; $-1.2\,\mu m$, $p < 0.01$) and SDMT ($0.1\,\mu m$, $p < 0.05$; $0.2\,\mu m$, $p < 0.05$; $0.2\,\mu m$, $p < 0.01$). A significant thickness loss compared with HCs was seen in the average pRNFL and in all quadrants except for the superior quadrant of primary progressive MS. The largest reduction compared with HCs was seen in the temporal pRNFL of PPMS eyes ($-15.8\,\mu m$; $p < 0.001$).
Conclusion: The reduction of average pRNFL, inferior pRNFL and temporal pRNFL thickness is associated with physical and cognitive disability in MS. We suggest the use of temporal pRNFL as a more sensitive outcome as it showed the strongest association to both EDSS and SDMT.

1. Introduction

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) characterized by a relapsing focal inflammation in multiple sites of the CNS, but in addition a low grade chronic disseminated inflammation affecting large parts of the CNS. The consequence is demyelination of nerve fibers, damage to axons and oligodendrocytes and glial scarring. Although disease progression in MS was originally seen as a result of focal demyelination, axonal degeneration has been recognized as the main determinant of irreversible disability (Bjartmar et al., 2003; Compston and Coles, 2008).

Slow progressive loss of optic nerve axons and retinal ganglion cells has been shown with optical coherence tomography (OCT) in MS patients with and without a history of optic neuritis (ON) and even in very early stages of the disease (Balk et al., 2016; Gelfand et al., 2012; Talman et al., 2010).

Peripapillary retinal nerve fiber layer (pRNFL) thickness has been suggested to be a valid structural marker of neurodegeneration in MS (Britze and Frederiksen, 2018).

In 2008 Toledo and co-workers reported the temporal thickness of pRNFL to be associated with physical disability (Toledo et al., 2008). This finding was recently supported by Graham et al. suggesting the progressive loss of axons seen in MS patients is more pronounced in the temporal pRNFL segment compared to average pRNFL thickness in relapsing remitting MS (RRMS) patients (Graham et al., 2016). It is not yet fully established whether temporal pRNFL, or thickness values from any of the other quadrants obtained with SD-OCT, correlates with clinical features of MS, such as disease subtype, physical disability, cognitive impairment and patient reported outcomes.

Therefore, the aim of the current study was to characterize the pattern of the pRNFL loss in different MS subtypes and to investigate the association between pRNFL and physical disability and cognitive impairment.

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Table 1
Demographics.

	Controls (n = 168)	RRMS (n = 336)	SPMS (n = 112)	PPMS (n = 17)
Age at OCT date (mean ± SD)	42.3 ± 15.4	38.9 ± 9.7	53.8 ± 10.0	50.2 ± 13.2
Sex (% female)	76.7	70.8	65.4	55.6
Disease duration (mean years ± SD)		9.1 ± 7.2	21.8 ± 9.4	10.6 ± 8.3
Disease modifying treatment duration 1st line (mean years ± SD)		2.8 ± 37	5.6 ± 6.3	2.5 ± 5.0
Disease modifying treatment duration 2nd line (mean years ± SD)		1.4 ± 2.1	1.3 ± 2.3	0.2 ± 0.4
EDSS median (interquartile range)		2.0 (1.5)	5.5 (2.8)	5.5 (2.0)
Previous history of ON in one eye,%		87 (26.5%)	24 (18.9%)	0 (0%)
Previous history of ON in both eyes,%		23 (6.2%)	8 (6.3%)	0 (0%)

EDSS = Expanded Disability Status Scale. RRMS = Relapsing-Remitting Multiple Sclerosis, SPMS = Secondary Progressive Multiple Sclerosis, PPMS = Primary Progressive Multiple Sclerosis, ON = Optic neuritis.
1st line disease modifying treatments includes: Interferon 1a, Interferon 1b and glatiramer acetate. 2nd line disease modifying treatments includes: natalizumab, fingolimod and rituximab.

2. Methods

2.1. Subjects

Ethical approval was given by the local ethics committee (Regional Ethics Committee in Stockholm) and the study followed the Declaration of Helsinki. All participants received written informed consents and approved by signature.

Patients diagnosed with MS, were recruited consecutively when attending their annual routine follow-up between May 2013 and October 2015 to the MS clinic of the Neurology Department at Karolinska University Hospital, Solna, Sweden. Patients were checked for a history of any ocular disease, trauma or systemic disease beside MS. When present they were excluded. In total, data from examinations of 465 MS patients were collected (about 95% of the solicited patients accepted to be included in the study). Patients were grouped according to disease course and history of ON. Demographic data, including disease modifying treatment duration were collected from records related the most recent visit in relation to the OCT examination. First line disease modifying treatments include interferon 1a, interferon 1b and glatiramer acetate. Second line disease modifying treatments include natalizumab, fingolimod and rituximab. Age was measured at the time of the OCT measurement. Physical disability level was graded according to the Expanded Disability Status Scale (EDSS), cognitive impairment was measured with Symbol Digit Modalities Test (SDMT) and Multiple Sclerosis Impact Scale 29 (MSIS – 29) was used for capturing patients' perception of disease severity. One hundred sixty-eight healthy and disease-free controls were recruited. A published study from our group, comparing the repeatability of two Spectral Domain OCT (SD-OCT) instruments, using the same OCT equipment/machine/device, provided normal data to the control group of this study (Brautaset et al., 2014).

2.2. Spectral domain optical coherence tomography

All subjects underwent SD-OCT examination using the Canon OCT-HS100 (Canon Europe, Amstelveen, Netherlands) which performs up to 70,000 A-scans/second with an axial resolution of 3 μm. The fixation target was a 2 mm wide cross and the scan mode "Disc 3D" was used. The optic disc scanning circle, which has a diameter of 3.45 mm and is centered on the optic disc, is built up of 256 B-scans, each composed of 512 A-scans, within a 10 × 10 mm area. Measurements were performed on both eyes of each patient. From the "Disc 3D" measurement the average pRNFL thickness for 360° around the optic disc was performed, as well as the pRNFL thickness for inferior, superior, nasal and temporal pRNFL quadrants around the optic nerve head. Only scans with a signal strength of ≥ 7 (maximum, 10), without artefacts caused by blinking or eye movements and in agreement with the OSCAR-1B criteria were selected for further analysis (Schippling et al., 2015; Tewarie et al., 2012). Scan analysis was done with Canon OCT-HS100 software version 4. The Advised Protocol for OCT Study Terminology and Elements (APOSTEL) recommendation was followed (Cruz-Herranz et al., 2016).

2.3. Statistical analysis

Data was summarised using mean (Standard Deviation (SD)) and median (Interquartile Range (IQR)). We used linear mixed effect models to compare the average pRNFL and pRNFL thickness in each quadrant (superior, inferior, temporal, nasal) between groups while accounting for within-patient inter-eye correlations. Since ON has already been shown to significantly impact the pRNFL thickness, all analyzes were controlled for previous history of ON in each eye. Models were adjusted for age and sex when pRNFL thicknesses in patients with MS were compared to healthy controls (HCs). OCT measures that significantly differentiated MS subtypes and HCs with the highest regression coefficient were considered optimal. In models confined to MS patients, we assessed the association between average pRNFL and pRNFL in each quadrant and the closest EDSS, MSIS-29 (both physical and psychological scales) and SDMT scores to the date of OCT scan using linear mixed effect models (EDSS, MSIS-29 and SDMT were performed within on average 1-month range from the date of OCT). All models were adjusted for sex, age, disease duration, disease subtype and previous history of ON and duration of exposure to first- and second-line disease modifying treatments for MS.

All statistical analyzes were performed in R version 3.3.2 using nlme package.

3. Results

A total of 465 MS patients were included; 336 (72%) with RRMS, 112 (24%) with secondary progressive MS (SPMS) and 17 (4%) with primary progressive MS (PPMS). A group with 168 HCs was also included. Demographic data is presented in Table 1. Table 2 presents pRNFL thickness in eyes of MS patients with different disease subtypes compared to HCs. The average difference in mean pRNFL was −6.4 μm (95% CI −8.5 to −4.3 μm, $p < 0.001$) in RRMS, −11.6 μm (95% CI −14.4 to −8.8 μm, $p < 0.001$) in SPMS and −10.7 μm (95% CI −16.0 to −5.5 μm, $p < 0.001$) in PPMS compared to HCs. Lower pRNFL thickness was seen in all quadrants in RRMS and SPMS. In PPMS eyes, a significant pRNFL thickness difference was seen in all quadrants except for the superior.

Lower pRNFL thickness is associated with higher EDSS score. The slope of reduction in pRNFL for each unit increase of EDSS score was significant for average pRNFL at 1.0 μm (95% CI −1.7 to −0.2, $p = 0.009$) and for temporal pRNFL by 1.2 μm (95% CI −2.0 to −0.5, $p = 0.002$) (Fig. 1). There was a borderline association between pRNFL thickness and the EDSS score in the inferior quadrant (−1.2 μm (95% CI −2.3 to 0.0, $p = 0.04$). The EDSS score was not associated with pRNFL thickness in superior and nasal quadrants (Table 2).

Table 2
Peripapillary retinal nerve fiber layer thickness difference. The values in the EDSS, SDMT and MSIS-29 boxes reflect best-fit slopes with units of: RNFL in microns/scale points, and these correlations were for the entire MS patient group.

	Peripapillary Retinal Nerve Fiber Layer thickness difference (μm)				
	Average	Quadrants			
		Superior	Nasal	Inferior	Temporal
Disease subtype[a]					
Healthy controls	Ref. 99 μm ± 9.7	Ref. 120 μm ± 13.8	Ref. 83 μm ± 14.7	Ref. 127 μm ± 16.6	Ref. 71 μm ± 11.1
Relapsing remitting	−6.4 (−8.5 to −4.3)***	−5.5 (−8.3 to −2.7)***	−5.9 (−10.5 to −3.9)***	−7.2 (−10.5 to −3.9)***	−7.6 (−9.8 to −5.3)***
Secondary progressive	−11.6 (−14.4 to −8.8)***	−11.2 (−19.0 to −8.4)***	−8.1 (−18.9 to −10.2)***	−14.5 (−18.9 to −2.3)***	−13.2 (−16.2 to −10.3)***
Primary progressive	−10.7 (−16.0 to −5.5)***	−4.7 (−11.9 to 2.4)	−10.7 (−18.9 to 2.3)***	−10.6 (−18.9 to −2.3)*	−15.8 (−21.4 to −10.1)***
EDSS[b]	−1.0 (−1.7 to −0.2)**	−0.8 (−1.8 to 0.2)	−0.7 (−1.5 to 0.1)	−1.2 (−2.3 to 0.0)*	−1.2 (−2.0 to −0.5)**
SDMT[b]	0.1 (0.0 to 0.2)*	0.1 (0.0 to 0.2)	0.0 (−0.1 to 0.1)	0.2 (0.0 to 0.3)*	0.2 (0.1 to 0.3)**
MSIS-29[b]					
Physical scale	−0.30 (−1.71 to 1.10)	−0.5 (−2.33 to 1.36)	0.1 (−1.45 to 1.69)	−0.9 (−3.07 to 1.30)	0.1 (−1.35 to 1.47)
Psychological scale	0.1 (−1.12 to 1.35)	−0.1 (−1.68 to 1.55)	−0.1 (−1.45 to 1.30)	0.3 (−1.65 to 2.19)	0.4 (−0.79 to 1.68)

*For $p < 0.05$, ** for $p < 0.01$, and *** for $p < 0.001$.
[a] Models adjusted for age, sex and previous history of optic neuritis.
[b] Models include MS patients only and were adjusted for MS subtype, disease duration, age, sex, duration of exposure to first- and second-line treatments and previous history of optic neuritis.

Lower pRNFL was also associated with cognitive dysfunction, as measured by SDMT. For every point of decrease in SDMT score the slope of reduction of average pRNFL was 0.1 μm (95% CI 0.0–0.2, $p = 0.02$), 0.2 μm (95% CI 0.1–0.3, $p = 0.003$) for temporal pRNFL (Fig. 2) and 0.2 μm (95% CI 0.0–0.3, $p = 0.01$) for the inferior quadrant. The corresponding values for superior and nasal quadrants were 0.1 μm (95% CI 0.0–0.2, $p = 0.1$) and 0.0 μm (95% CI −0.1 to 0.1, $p = 0.7$), respectively.

There was no association between MSIS-29 physical or psychological scores and any pRNFL measurement (Table 2). Eyes with prior ON (MSON+) were shown to have more severely reduced pRNFL thickness compared to MS eyes without a history of ON (MSON-). The unaffected fellow eye of MSON+ had a thickness reduction similar to eyes of patients without a history of ON (MSON-). MSON- eyes had an average thickness value of 93 μm, ranging from 59 to 126 μm. MSON+ eyes and their unaffected fellow eyes had an average thickness of 80 μm (ranging

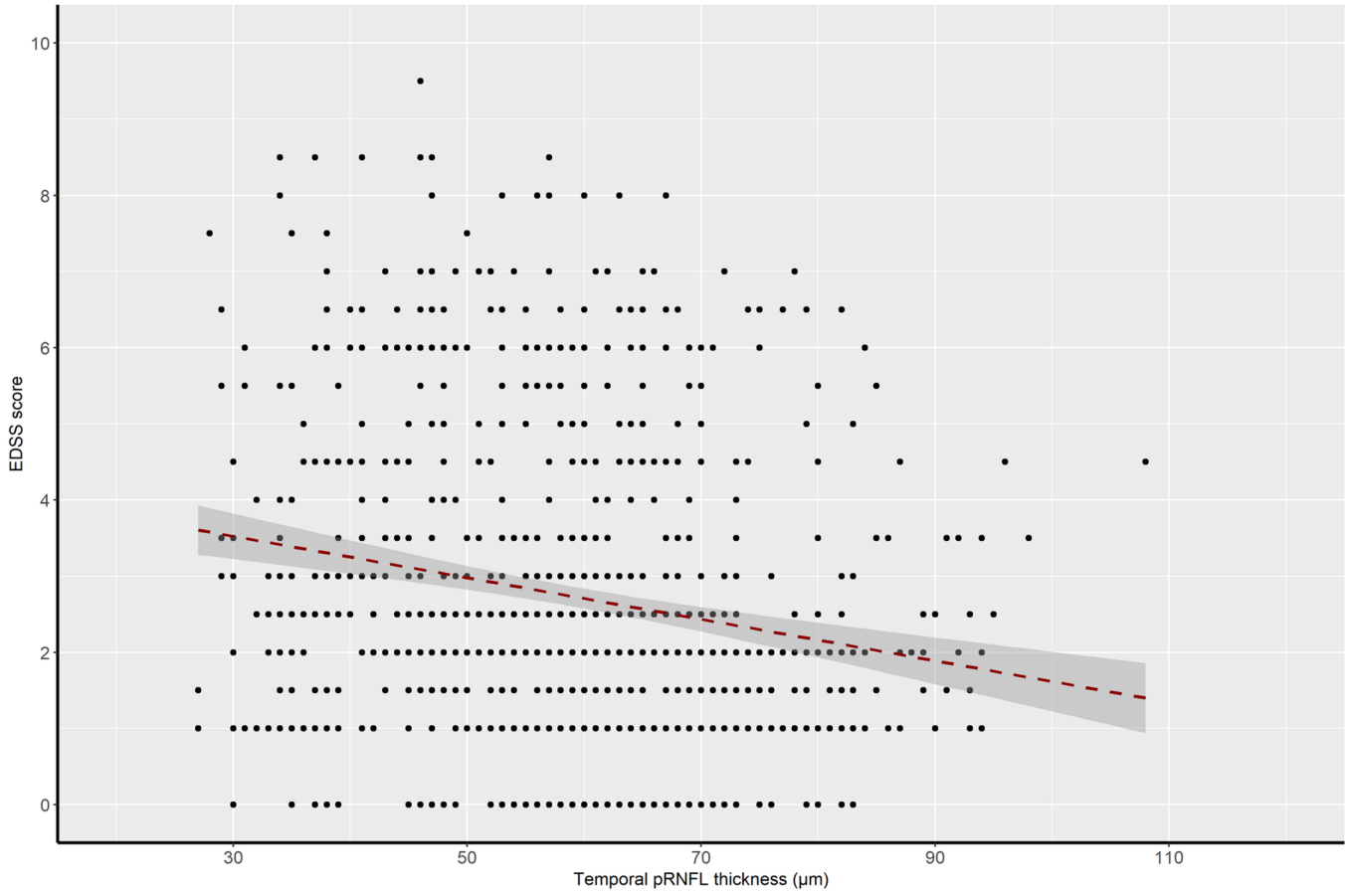

Fig. 1. Graph showing the correlations between temporal peripapillary retinal nerve fiber layer thickness (Temporal pRNFL) and Expanded Disability Status Scale (EDSS).

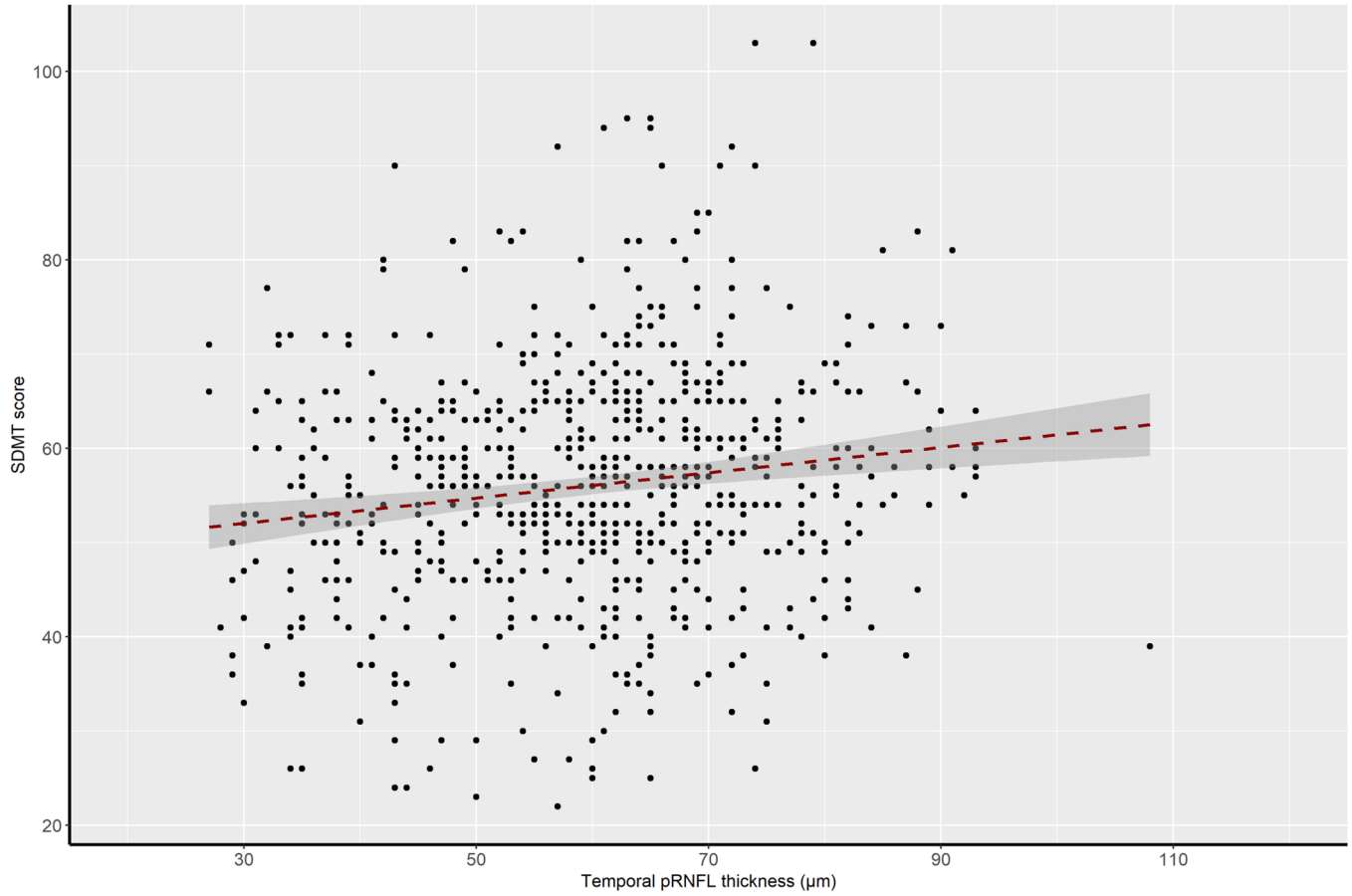

Fig. 2. Graph illustrating the correlations between temporal peripapillary retinal nerve fiber layer thickness (Temporal pRNFL) and Symbol Digit Modalities Test (SDMT).

between 48 and 115 μm) and 94.5 μm (ranging between 64 and 119 μm) respectively. The eyes of HCs had an average thickness of 99 μm, ranging from 78 to 125 μm.

4. Discussion

By assessing a large cohort of MS patients with a high-resolution OCT, we report that significant retinal changes in MS with pRNFL thinning is associated with physical disability and cognitive impairment. In our cohort, each unit increase of EDSS score was significant with significant lower in average pRNFL. Similarly, lower average pRNFL thickness was also associated with higher cognitive dysfunction, as measured by the SDMT score. Our results also indicate that the temporal pRNFL is the most consistently affected quadrant showing the highest correlation with MS subtype, physical disability and cognitive impairment.

Magnetic resonance imaging (MRI) is considered the gold standard imaging tool for monitoring MS. Both EDSS and SDMT have been previously shown to correlate with measures of axonal and neuronal loss of CNS, such as brain volume loss (Filippi et al., 2010; Fisher et al., 2002; Rao et al., 2014). OCT has been suggested to complement MRI for monitoring disease progression (Frohman et al., 2009; Garcia-Martin et al., 2017; Martinez-Lapiscina et al., 2016). Interestingly, clear correlations with both EDSS and SDMT were found for average pRNFL thickness in the present study. There are several studies investigating the association between pRNFL and EDSS (Garcia-Martin et al., 2014; Gordon-Lipkin et al., 2007; Lange et al., 2013; Martinez-Lapiscina et al., 2016; Oberwahrenbrock et al., 2012; Saidha et al., 2011; Toledo et al., 2008). The results have varied, and no universal association has been found for all MS subtypes. A relationship between worsening on the EDSS scale and pRNFL thinning measured with OCT was recently reported and is in line with our results (Garcia-Martin et al., 2017).

The relationship between cognitive impairment and different OCT measures has so far only been sparsely investigated. Coric and coworkers recently reported a significant association between average pRNFL and cognitive impairment in MS (Coric et al., 2017).

In a previous study (Graham et al., 2016) it was found that the temporal pRNFL showed the best sensitivity in detecting progressive pRNFL thinning in MS patients. This study expressively included RRMS and the cohort consisted of 45 MS patients and 20 age-matched controls. Our results from a large cohort of MS patients, with all subtypes represented, also indicate that the temporal pRNFL is the most consistently affected quadrant, especially in PPMS patients according to the high regression coefficient. However, the other pRNFL parameters (except the superior quadrant of pRNFL thickness in PPMS) were also found to statistically differ, i.e., differentiated all MS subgroups from HCs. These results are in accordance with other studies (Gelfand et al., 2012; Oberwahrenbrock et al., 2012; Pulicken et al., 2007). The atrophy of the different pRNFL quadrants is not equally distributed and therefore we suggest that the temporal pRNFL is added to average pRNFL as a separate parameter when searching for existing associations.

It has been previously shown that lesions engaging the optic radiation can cause retrograde transynaptic degeneration of the pRNFL and partly explain the progressive pRNFL thinning seen in MS patients (Albrecht et al., 2012; Balk et al., 2015; Klistorner et al., 2017; Reich et al., 2009). Such lesions can partially explain our findings regarding reduced pRNFL thickness.

It is not known why the temporal pRNFL is generally more reduced in thickness compared to the other quadrants. It has been shown in post

mortem tissue by Evangelou and colleagues that the parvocellular axons were selectively more reduced in quantity in MS eyes (Evangelou et al., 2001). This is possibly because they are the thinnest axons and therefore more vulnerable.

As expected, a more severe loss of pRNFL thickness was found in eyes with ON history, which is in line with previous studies (Petzold et al., 2017, 2010). In addition, we studied the unaffected fellow eye of MSON+ in order to investigate if the pRNFL reduction was more pronounced in those eyes than in MSON- eyes. It has been suggested that a lesion due to ON might spread to the chiasm and cause thinning of the pRNFL in the fellow eye (Klistorner et al., 2014). We found that the pRNFL was reduced in the fellow eye of MSON+ (~4 μm thinner than HCs), however the thickness reduction was not more severe than in MSON- eyes (6 μm thinner than HCs).

Strengths with this cross-sectional study were the large sample size from one single neurology centre and the possibility to include all MS subtypes. The measurements were also performed with an SD-OCT that offers high spatial resolution. A possible limitation of this study was that ON history was collected from medical records and the patient-reported history. There might be a chance that borderline clinical episodes of ON have gone unnoticed, however this is a common feature with most other studies in the field and not likely to have influenced the results on group level.

In conclusion, pRNFL thickness reduction in MS is significantly associated with physical and cognitive disability and OCT measurements are useful for axonal loss. We suggest the use of temporal pRNFL thickness as a more sensitive outcome as oppose to the average pRNFL thickness.

Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

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