Optical Coherence Tomography and Visual Evoked Potentials as Prognostic and Monitoring Tools in Progressive Multiple Sclerosis

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Understanding the mechanisms underlying progression and developing new treatments for progressive multiple sclerosis (PMS) are among the major challenges in the field of central nervous system (CNS) demyelinating diseases. Over the last 10 years, also because of some technological advances, the visual pathways have emerged as a useful platform to study the processes of demyelination/remyelination and their relationship with axonal degeneration/protection. The wider availability and technological advances in optical coherence tomography (OCT) have allowed to add information on structural neuroretinal changes, in addition to functional information provided by visual evoked potentials (VEPs). The present review will address the role of the visual pathway as a platform to assess functional and structural damage in MS, focusing in particular on the role of VEPs and OCT, alone or in combination, in the prognosis and monitoring of PMS.

Keywords: multiple sclerosis, progressive multiple sclerosis, visual pathway, visual evoked potentials, optical coherence tomography

BACKGROUND

The Challenge of Progressive Multiple Sclerosis

Multiple sclerosis (MS) is a chronic inflammatory, immune-mediated disease of the central nervous system (CNS; Ontaneda and Fox, 2015), characterized by demyelination, axonal loss, and neurodegeneration. Although the pathophysiology underlying the different phenotypes still needs to be clarified, four main clinical courses of the disease have been identified: relapsing–remitting MS (RRMS; characterized by clearly defined neurological exacerbations with full or incomplete recovery, in the presence of dissemination in space and time of the inflammatory process among the CNS), clinically isolated syndrome (CIS; a first neurological episode suggestive of MS, but formal criteria of dissemination in time are not fulfilled), secondary progressive MS (SPMS; defined retrospectively by the occurrence of gradual disability worsening with or without occasional relapses, minor remissions, and plateaus, following an initial RRMS course), and primary progressive MS (PPMS; characterized by progressive accumulation of disability from disease onset with occasional plateaus, temporary minor improvements, or acute relapses still consistent with the definition; Lublin and Reingold, 1996; Lublin et al., 2014). The MS courses can be further qualified by the presence/absence of disease activity [presence of relapses and/or magnetic resonance imaging (MRI) activity – i.e., gadolinium-enhancing lesions or...
new/unequivocally enlarging T2 hyperintense lesions] and by the disability state: worsening, improving, or stable (Lublin et al., 2014).

The pathological key features underlying the clinical expression of the disease can be depicted as a spectrum, ranging from waves of acute focal inflammation in RRMS to predominant neurodegenerative features with concomitant chronic compartmentalized inflammation in progressive multiple sclerosis (PMS) (Lassmann et al., 2007; Giovannoni et al., 2016).

During the past decades, a major progress has been made in understanding disease mechanisms in RRMS, with inflammation and subsequent focal demyelination with breakdown of the blood–brain barrier representing the main driver of clinical disease in this subset of patients. This knowledge has led to the development of anti-inflammatory and immunomodulatory treatments that effectively reduce the severity and frequency of new demyelinating episodes (Diebold and Derfuss, 2016). In PMS, instead, focal disruption of the blood–brain barrier is less common, and widespread degeneration of the white and gray matter variably combined with slow expansion of chronically active lesions are the pathological hallmarks (Lassmann, 2017). Several and non-necessarily exclusive mechanisms have been proposed to explain the pathogenesis of PMS (i.e., compartmentalized ongoing chronic inflammation, chronic inflammation leading to inflammation-independent neurodegeneration, and primary neurodegeneration amplified by concurrent independent inflammation), with SPMS and PPMS course likely sharing similar pathophysiological features (Confavreux and Vukusic, 2006; Trapp and Nave, 2008; Frischer et al., 2009; Lassmann et al., 2012). Fundamental pathogenetic pathways responsible of clinical progression, however, still remain unidentified, with no available accurate preclinical model reproducing this stage of the disease. The approval of Ocrelizumab for active PPMS and SPMS treatment (Montalban et al., 2017), and of Siponimod for active SPMS by EMA and for relapsing MS by FDA (Kappos et al., 2018), represent important encouraging novelties, but the tangible real-world impact of these molecules has still to be assessed especially in the absence of overt inflammation (Montalban et al., 2017; Kappos et al., 2018). Unfortunately, previous studies exploring neuroprotective strategies have failed; however, some positive results have recently emerged from phase III clinical trials and are now under exploration in definite clinical trials (Ontaneda et al., 2015; Sorensen et al., 2020). Moreover, the process of discovery of new therapeutic targets for PMS is a priority of the International Progressive MS Alliance (2021), a multistakeholder initiative promoted by International Federation of Multiple Sclerosis and MS patient associations.1

### The Visual Pathway as a Model of Brain Damage in Multiple Sclerosis

In order to succeed in the challenge represented by PMS, our ability to early detect the pathological processes on the stage will be of fundamental importance. At present, diagnosis of PMS is mainly retrospective since imaging methods as well as other biomarkers to catch or predict progression are not well established (Correale et al., 2017). There is an unmet need for new strategies to identify inflammation/demyelination and particularly neurodegeneration in a subclinical phase, with consequent prompt interventions aimed to prevent disability to occur for our patient.

Emerging evidence suggests that the visual system may play an important role in this game (Martinez-Lapiscina et al., 2014). The visual pathway is in fact frequently involved in MS, with visual dysfunction that is not only common but also highly relevant (Fisher et al., 2006; Heesen et al., 2008; Chatziralli et al., 2012). Furthermore, the visual pathway may represent a model of both acute focal CNS damage [through acute optic neuritis (ON) and retinal periphlebitis] (Albrecht et al., 2007; Siger et al., 2008), as well as a model of chronic, diffuse CNS involvement (through chronic retinopathy, optic neuropathy, and trans-synaptic degeneration). The ongoing pathological processes can be accurately evaluated due to the availability of highly sensitive imaging [i.e., MRI or optical coherence tomography (OCT)] and electrophysiological [i.e., visual evoked potentials (VEPs) and electroretinography (ERG)] tests. The combination of these techniques allows to describe the interactions between the different processes at play (such as inflammation, demyelination, and axonal and neuronal loss) in vivo and in a non-invasive way, features that identify the visual pathway as an elective platform to differentiate MS pathophysiology from other inflammatory conditions of the CNS (Vabanesi et al., 2019), as well as a reliable model to monitor the disease and to test new neuroprotective or regenerative therapies in the context of clinical trials (Fisher et al., 2006; Heesen et al., 2008; Chatziralli et al., 2012; Martinez-Lapiscina et al., 2014; Villoslada, 2016).

Optical coherence tomography in MS has been widely used to measure in particular retinal nerve fiber layer (RNFL) and ganglion cell–inner plexiform layer (GCIPL) thickness as markers of neuroaxonal loss, allowing to detect subclinical neurodegeneration (Petzold et al., 2010; Alonso et al., 2018; Costello and Burton, 2018). RNFL and GCIPL thickness have been correlated with tests of visual function (Pulicken et al., 2007; Pueyo et al., 2008; Zaveri et al., 2008), with global disability scores such as Expanded Disability Status Scale (EDSS; Albrecht et al., 2007; Siger et al., 2008), with functional measures as those provided by VEPs (Klistorner et al., 2008; Pueyo et al., 2008; Di Maggio et al., 2014), but also with cerebral and optic nerve MRI parameters (Triep et al., 2006; Graziali et al., 2008; Siger et al., 2008), as well as with fluid biomarkers such as serum neurofilament light chain concentration (Tavazzi et al., 2020). Most of the evidence available in the field is actually related to the RRMS course, with neuroretinal atrophy being associated with disease activity (Pisa et al., 2017), but with the possibility to detect RNFL and GCIPL thinning over time in MS patients with progression independent of relapse activity (PIRA; Bsteh et al., 2020; Pisa et al., 2020). Cross-sectional RNFL, total macular volume (TMV), and GCIPL thickness measures independently predicted long-term disability in large cohorts of predominately RRMS patients (Martinez-Lapiscina et al., 2016; Rothman et al., 2019; Lambe et al., 2021), while the application of mathematical models has suggested RNFL evolution, resulting from a mix of

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inflammatory and degenerative processes, to accurately reflect disability progression over time (Montoliu et al., 2019).

More recently, other retinal layers have also received attention as possible biomarkers in MS: in particular, inner nuclear layer (INL) consists of a network of bipolar, amacrine, and horizontal cells; despite some signs of atrophy have been described on histopathology at this level in MS (Green et al., 2010), in vivo studies did not show an extensive INL atrophy as in the case of RNFL and GCIPL, even after ON (Seigo et al., 2012; Syc et al., 2012). Pathology studies have identified inflammation and microglial activation within the inner retina in MS patients (Green et al., 2010), and in vivo observations also suggest INL as a possible biomarker of inflammation within the CNS, with increased INL thickness reflecting a condition of retinal inflammation, which parallels brain inflammatory activity in MS: microcystic macular edema (MME) within this layer has in fact been described to be associated with ON and disability; furthermore, increased INL thickness has been associated with a greater risk of developing new T2 or gadolinium-enhancing lesions and of new relapses (Saïdha et al., 2012; Balk et al., 2019); finally, successful response to disease-modifying treatments (DMTs) has been associated with a sustained reduction of INL volume (Knier et al., 2016). Other authors, however, have postulated the possibility for INL thickening (and MME in particular) to be related to vitreomacular tractions, Müller cell pathology, subclinical uveitis, or retinal periphlebitis, conditions possibly found in association with MS (Kerrison et al., 1994; Chen and Gordon, 2005). Significant correlations between INL thickening and RNFL/GCIPL thinning have been also described: according to this evidence, it has been speculated that INL enlargement is related to structural changes in other retinal layers (as the result of the opposing tractions between inner limiting and Bruch’s membranes), being therefore compensatory in nature (Kaushik et al., 2013).

Magnetic resonance imaging (MRI) can be used to identify inflammation (lesion load on T2-weighted images and gadolinium-enhancing lesions on T1-contrast sequences), but also (with 3D high-resolution T1-weighted images) to quantify regional atrophy along the visual pathway, such as optic nerve atrophy after ON, of the lateral geniculate nucleus (LGN) at the thalamic level and of the visual cortex (Gabilondo et al., 2014). Other MRI parameters such as the magnetization transfer ratio (MTR) and the diffusion-weighted imaging (DWI) are sensitive to microstructural damage, allowing to characterize demyelination and axonal damage along the visual pathway, with an association with visual function measures (Melzi et al., 2007; Naismith et al., 2010; Kolbe et al., 2012). In the following sections, possible relations between OCT-VEPs parameters and MRI data have been assessed; however, an extensive dissertation of MRI findings and their implications in PMS is beyond the purpose of the present review.

Among functional techniques, traditional full-field VEPs (ff-VEPs) can be performed as an indicator of demyelination/remyelination, expressed by latency delay/shortening of the major component P100, with potential diagnostic, prognostic, and monitoring roles in MS (Comi et al., 1999; Leocani et al., 2018). In addition, multifocal techniques (mf-VEPs) allow to assess conduction for separate portions of the visual field, providing information about local signals of small areas occupying up to 24 central degrees of the visual field, with the possibility to detect mild abnormal local responses and scotomas (Klistorner et al., 2008).

Starting from this background, in this article, we wanted to assess the real value of the visual pathway as a specific biomarker of functional and structural damage in PMS patients, focusing in particular on VEPs and OCT use as possible prognostic and monitoring tools.

**EVIDENCE ACQUISITION**

We searched PubMed up to March 15, 2021, using the following terms: “Progressive Multiple Sclerosis and Visual Evoked Potentials,” “Progressive Multiple Sclerosis and Optical Coherence Tomography,” “Optical Coherence Tomography and Disability and Multiple Sclerosis,” and “Visual Evoked Potentials and Disability and Multiple Sclerosis.”

**VISUAL EVOKED POTENTIALS IN PMS**

There is little specific information about VEPs in PMS, and especially PPMS, because many studies on VEPs in MS were performed prior to the current classification of disease courses (Lublin et al., 2014).

Currently available data on ff-VEPs sensitivity mainly derive from studies assessing the role of a multimodal neurophysiological assessment in MS cohorts, including subsets of PMS patients. Leocani et al. (2006) performed a study in which, among the others, 41 PMS patients (13 PPMS and 28 SPMS) underwent multimodal evoked potentials including ff-VEPs, with high rates of visual conduction impairment in both subgroups (92.3% for PPMS and 85.7% for SPMS), significantly more elevated than the abnormalities recorded among the RRMS cohort (77.4%; Leocani et al., 2006). These findings were consistent with those deriving from other previous experiences: in a small Japanese cohort of 11 PPMS patients, higher frequencies of VEPs abnormality were reported in comparison with 35 RRMS patients (Kira et al., 1993). In a similar way, data extrapolated from a European cohort of 156 PPMS patients showed a delay of conduction along the visual pathway in 105 out of 131 subjects (80%) who had undergone ff-VEP examination (Stevenson et al., 1999); VEP studies in PMS patients are summarized in Table 1. The high frequency of abnormal ff-VEPs in PPMS, asymptomatic in the vast majority of the cases, allowed to reveal a clinically unsuspected spatial dissemination of the disease, and ff-VEPs were therefore once included among PPMS diagnostic criteria (Thompson et al., 2000). Multifocal VEP is a new technique that provides high sensitivity and specificity in detecting abnormalities in visual function in MS patients (Laron et al., 2009); however, no specific information exploring their role in PMS is currently available in literature to the knowledge of the authors.

Backner et al. (2019) analyzed the relations between different vision-related measures, including ff-VEPs, in PMS. In particular,
they reported data related to a cohort of 48 PMS patients (classified as 18 progressive with relapses, 21 SPMS, and nine PPMS) who had been enrolled in a longitudinal mesenchymal stem cell therapy study (NCT02166021), conducted at the Hadassah-Hebrew University Medical Center. Significant inverse correlations were found between motion perception tests [object for motion (OFM) and number for motion (NFM)] and ff-VEPs latency in eyes with previous ON and their fellow eyes, in the presence of preserved visual acuity (VA), thus confirming previous evidences suggesting that dynamic visual functions may reflect myelination levels along the visual pathway (Raz et al., 2014). Considering instead functional and structural measures, a correlation between ff-VEPs latency on the one hand and RNFL thickness as well as optic radiation lesion load on the other was described in non-ON eyes of the same cohort of patients enrolled in the NCT02166021 trial (Berman et al., 2020). In this regard, Davies et al. (1998) had previously reported optic nerve lesion length and area [detected by MRI on the short tau inversion recovery (STIR) sequence], to significantly correlate with ff-VEP latency prolongation in a cohort of 25 SPMS patients, only four of whom had a history of acute ON.

When considering the specific prognostic role of VEPs in PMS, available data are even more limited. Sater et al. (1999) proposed ff-VEPs as a tool to assess disease progression in addition to standard disability-based endpoints: obtaining serial VEPs and MRI scans from 11 PMS patients over a 1.5-year period, they found in fact no significant change in disability as measured by EDSS and Ambulation Index, nor in MRI T2 plaque burden, in the presence, however, of a significant progression of the P100 latency over time (Sater et al., 1999). More recently, Schlaeger et al. (2014) prospectively investigated the role of VEPs in the context of a multimodal evoked potential assessment as possible predictors of disease course in a small cohort of PPMS patients; they found that a multimodal evoked potential score correlated with disability in these patients, also allowing some prediction of the course of the disease.

**OPTICAL COHERENCE TOMOGRAPHY IN PMS**

Several studies over the last 15 years examined cross-sectionally the pattern of retinal axonal loss (expressed by RNFL measurement at a peripapillary level), across the different MS clinical subtypes also including subsets of PMS patients, often coming to partially contrasting conclusions. As a premise, it is important to notice that early studies measured RNFL thickness through time-domain OCT devices (TD-OCT), while more recent experiences have been made with next-generation OCT based on spectral-domain technology (SD-OCT). This innovation allowed not only to increase speed acquisition but also to improve resolution power and reproducibility; segmentation algorithms also differ between TD-OCT and SD-OCT devices; therefore, results obtained with different OCT generations are not interchangeable and directly comparable (Bock et al., 2010).

In 2007, Pulicken et al. (2007) obtained RNFL thickness measures using a TD-OCT device (OCT-3, Zeiss Meditec) on a cohort of 135 RRMS, 16 SPMS, and 12 PPMS patients, as well as in 47 healthy controls: the three subgroups of MS patients all showed decreased RNFL values in comparison with controls; compared with RRMS, both SPMS and PPMS patients revealed a trend toward thinner RNFL values although in the absence of a statistical significance, probably due to the small number of PMS patients included in the study. In 2008, Henderson et al. (2008) performed a similar study (using TD-OCT Stratus, Zeiss Meditec) on 27 SPMS and 23 PPMS patients, with the former but not the latter showing reduced RNFL thickness values when compared with 20 healthy controls, in the absence of significant differences between the two PMS subgroups when age-adjusted regression coefficient of RNFL thickness was directly compared (although in the presence of lower values among SPMS patients); significant correlations between RNFL values and VA measures were also reported, especially in the PPMS cohort. In another study using the same TD-OCT device (Stratus) published in 2010, Siepman et al. (2010) reported no statistically significant difference in terms of mean RNFL thickness comparing 26 RRMS and 29 PMS patients. In 2012, Gelfand et al. (2012) published retinal imaging data obtained in 60 SPMS and 33 PPMS patients, using a new SD-OCT device (Spectralis, Heidelberg Engineering): the authors reported similar RNFL thickness values between SPMS and PPMS patients examining eyes without previous ON, with TMV slightly lower in the PPMS group. These results were consistent with those published by Albrecht et al. (2012), including 41 SPMS and 12 PPMS patients: using the same Spectralis device, the authors reported significant RNFL thinning compared with healthy controls for both subgroups, although a direct comparison between different PMS subsets was not performed. Another coeval work performed with Spectralis on a German cohort of 414 MS patients (308 RRMS, 65 SPMS, and 41 PPMS) and 94 healthy controls reported significant differences in terms of RNFL thickness only between RRMS and SPMS patients after adjusting for clinical–demographic parameters (such as age,
increasing attention has been directed toward the analysis of other retinal strata (particularly GCIPL) measured on macular scans; initial specific information is becoming available also for PMS cohorts. Some of the studies previously described already took into account these aspects: Albrecht et al. (2012) performed a manual segmentation of macular scans, reporting reduced GCIPL values in both SPMS and PPMS patients compared with controls; in PPMS subgroup, a significant reduction of the INL was also reported but not confirmed after the exclusion from the analysis of eyes with previous ON. Balk et al. (2014), using instead an automated software program, showed GCIPL to be significantly reduced among PPMS patients when compared with SPMS, also in the absence of previous ON history. Another work published in 2017 using SD-OCT (Cirrus 5000, Zeiss Meditec) compared 29 PMS with 84 RRMS patients, showing in the former subgroup significantly reduced thickness values not only for GCIPL but also when considering outer plexiform layer (OPL); included patients, however, were of non-Caucasian origin (Behbehani et al., 2017). Cross-sectional OCT studies assessing retinal layers in PMS are summarized in Table 2.

Researchers also focused on exploring the relation between retinal measures and clinical parameters; available data, however, are often non-specific for PMS, with major contributions (relative to visual function and global disability measures) deriving from some of the studies previously reported. Henderson et al. (2008) found a relationship between VA (both high- and low-contrast tests) and RNFL thickness in their PMS cohort, with particularly robust data in PPMS patients, as also suggested by

| Study | Device | Cohort | Main findings |
|-------|--------|--------|---------------|
| Pulicken et al., 2007 | TD-OCT (OCT-3, Zeiss Meditec) | 1 3 5 RRMS, 16 SPMS, 12 PPMS, 47 HC | RNFLt reduced in MS groups compared to HC; statistical trend indicating thinner RNFLt in SPMS and PPMS compared to RRMS |
| Henderson et al., 2008 | TD-OCT (Stratus, Zeiss Meditec) | 2 7 SPMS, 23 PPMS, 20 HC | Mean RNFLt reduced in SPMS (but not PPMS) compared to RRMS |
| Siepman et al., 2010 | TD-OCT (Stratus, Zeiss Meditec) | 26 RRMS, 10 SPMS, 29 PPMS | Mean RNFLt no statistically different between RRMS and PPMS patients |
| Gelfand et al., 2012 | SD-OCT (Spectralis, Heidelberg Engineering) | 4.5 CIS, 403 RRMS, 60 SPMS, 33 PPMS, 53 HC | Mean RNFLt similar in SPMS and PPMS patients in non-ON eyes; TMV slightly lower in PPMS group |
| Albrecht et al., 2012 | SD-OCT (Spectralis, Heidelberg Engineering) | 4 2 RRMS, 41 SPMS, 12 PPMS, 95 HC | Mean RNFLT and GCIPLt reduction in both SPMS and PPMS compared to HC; INLt reduction only in PPMS in comparison to HC |
| Oberwahrenbrock et al., 2012 | SD-OCT (Spectralis, Heidelberg Engineering) | 308 RRMS, 65 SPMS, 41 PPMS, 94 HC | Mean RNFLt lower in SPMS (but not PPMS) compared to RRMS; TMV reduced in both SPMS and PPMS compared to RRMS |
| Balk et al., 2014 | SD-OCT (Spectralis, Heidelberg Engineering) | 140 RRMS, 61 SPMS, 29 PPMS, 63 HC | Mean RNFLt, GCIPLt and INLt reduction in SPMS compared with PPMS but not RRMS considering non-ON eyes; highest absolute values in PPMS |
| Behbehani et al., 2017 | SD-OCT (Cirrus 5000, Zeiss Meditec) | 84 RRMS, 29 PMS, 38 HC (non-Caucasian) | Mean RNFLt, GCIPLt and OPLt reduced in PMS compared to RRMS patients |
| Jankowska-Lech et al., 2019 | SD-OCT (OCT 1000 Mark II, Topcon) | 26 RRMS, 22 PMS, 31 HC | Mean RNFLt reduced in PMS compared to RRMS patients only when taking into account ON eyes |

TD-OCT, time domain–optical coherence tomography; SD-OCT, spectral domain–optical coherence tomography; CIS, clinically isolated syndrome; RRMS, relapsing–remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; HC, healthy controls; RNFLt, retinal nerve fiber layer thickness; TMV, total macular volume; GCIPLt, ganglion cells–inner plexiform layer thickness; INLt, inner nuclear layer thickness; OPLt, outer plexiform layer thickness; ON, optic neuritis.
the observation (with SD-OCT Spectralis) of a significant relation between low-contrast VA and GCIPL thickness in another cohort of 25 PPMS patients (Poretto et al., 2017). The same authors, however, did not identify any significant relation between RNFL thickness and disease duration, duration of the progressive phase, nor with EDSS (Henderson et al., 2008). A lack of a correlation between RNFL thickness and EDSS has been also reported with SD-OCT Spectralis in a cohort of 28 non-Caucasian SPMS patients (Yousefipour et al., 2016). Siepman et al. (2010) reported instead similar relations between RNFL thickness and VA, also pointing out a negative correlation with EDSS in eyes without previous ON; data, however, were referred to the entire study cohort of 26 RRMS and 29 PPMS patients. Albrecht et al. (2012) expanded this analysis in their cohort of 95 MS patients (including 41 SPMS and 12 PPMS) observing EDSS to correlate also with macular thickness and OPL, interestingly with a positive correlation in this latter case. Behbehani et al. (2017) reported instead an inverse correlation between ONL thickness and EDSS in 29 PMS patients. No significant correlation with RNFL (measured with Spectralis) was instead identified when considering motion perception tests, which appear to be mainly related to myelination status along the visual pathway more than to axonal loss (Backner et al., 2019). Finally, considering the possible relation between OCT measures and other clinical parameters, Coric et al. (2018) analyzed with Spectralis a cohort of 217 MS patients (including a remarkable percentage of PMS patients – 56 SPMS and 28 PPMS, respectively) describing cognitively impaired patients to have significantly reduced RNFL and GCIPL values.

Moving to assess the relation between OCT and other instrumental parameters, in 2007, Gordon-Lipkin et al. (2007) had already described RNFL thickness (measured with OCT-3) to correlate with brain atrophy in 40 MS patients (20 RRMS and 20 PMS), although this association appeared to be driven by the RRMS subset and by cerebrospinal fluid more than white or gray matter volume. In another cohort of 25 PPMS patients (assessed with Spectralis), RNFL thickness revealed to be associated with thalamus and visual cortex volume, while GCIPL values were associated with cortical lesion load; the authors suggested retrograde trans-synaptic degeneration and/or a common pathophysiologic process affecting both the brain and the retina as possible explanations (Petracca et al., 2017). Data deriving from a recent Italian retrospective study including a cohort of 84 PMS patients also revealed increased values of INL thickness in a subset of patients who had shown MRI activity during the year before OCT assessment (Spectralis), proposing INL evaluation as a possible surrogate marker of disease activity also among progressive patients (Cellerino et al., 2019). Saidha et al. (2015) explored the relation between SD-OCT (Cirrus 4000, Zeiss Meditec) and MRI parameters longitudinally in the context of a 4-year study including 107 MS patients: the authors described RNFL and GCIPL thinning to be significantly associated with whole-brain, and gray and white matter atrophy, pointing out a stronger relation in the subset of 36 PMS patients. However, data extrapolated from a randomized placebo-controlled trial testing the possible role of lipoic acid in SPMS showed only modest correlations between RNFL and cortical gray matter atrophy in a subset of 51 patients with OCT (Cirrus 5000) and MRI longitudinal data available, with no significant results for GCIPL (Winges et al., 2019). In the SPRINT MS phase II clinical trial, however, ibudilast significantly reduced over 2 years the progression of brain atrophy compared with placebo in PMS patients; this positive result was supported by a trend for a lower RNFL thickness reduction in ibudilast-treated patients (Fox et al., 2018). Finally, OCT parameters have been also analyzed in association with other functional instrumental techniques: in particular, a correlation between RNFL thickness and ff-VEPs latency has been identified in PMS patients considering eyes without ON history (Backner et al., 2019).

The evolution over time of OCT parameters has also started to be explored in different subsets of MS patients, but conclusive specific data for PMS are still lacking. In a work published

| Study | Device | Cohort | Follow-up | Main findings |
|-------|--------|--------|-----------|--------------|
| Talman et al., 2010 | TD-OCT (OCT-3, Zeiss Meditec) | 299 MS (84% RRMS) | 1.5 years (range 0.5–4.5) | RNFLt reduction as a function of time (average −2.9 µm at 2–3 years and −6.1 µm at 3–4.5 years) in some patients with MS, even in the absence of aON |
| Henderson et al., 2010 | TD-OCT (Stratus, Zeiss Meditec) | 18 SPMS, 16 PPMS, 18 HC | 1.5 years (range 1.1–2.4) | No significant RNFLt reduction over time in patients and controls. TMV decline in both groups, with no between-group differences |
| Balk et al., 2016 | SD-OCT (Spectralis, Heidelberg Engineering) | 7 Cis, 89 RRMS, 26 SMPS, 13 PPMS, 16 HC | 2 years | RNFLt and GCIPLt reductions more pronounced early in the course of disease (higher atrophy rate in RRMS than SPMS patients) |
| Winges et al., 2019 | SD-OCT (Cirrus 5000, Zeiss Meditec) | 51 SPMS | 2 years | RNFL (−0.31 µm/year) and GCIPL (−0.29 µm/year) atrophy rates similar in aON and nonON eyes; RNFLt > 75 µm associated with higher (−0.85 µm/year) rate |
| Sotichos et al., 2020 | SD-OCT (Cirrus HD-OCT, Zeiss Meditec) | 178 RRMS, 186 PMS, 66 HC | 3.7 years (IQ range 2.0–5.9) | PMS phenotype associated with faster RNFLt (−0.34%/year) and GCIPLt (−0.27%/year) reduction; no significant impact determined by DMTs |

**TD-OCT, time domain–optical coherence tomography; SD-OCT, spectral domain–optical coherence tomography; CIS, clinically isolated syndrome; RRMS, relapsing–remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; HC, healthy controls; RNFL, retinal nerve fiber layer thickness; TMV, total macular volume; GCIPL, ganglion cells–inner plexiform layer thickness; aON, acute optic neuritis; nON, non-optic neuritis; DMTs, disease-modifying treatments.**
rates (lipoic acid trial showed annualized RNFL and GCIPL atrophy such a relation was not identified for INL. Longitudinal data over longer disease duration), and consistently, they found RNFL and duration (with thinning rate becoming smaller in the presence of RNFL and GCIPL thinning to be significantly related to disease phenotype) with TD-OCT (OCT-3): the authors described progressive RNFL thinning as a function of time. In contrast with this finding, Henderson et al. (2010) using Stratus TD-OCT did not find any significant change of RNFL thickness over time in a small cohort of 34 PMS patients (18 SPMS and 16 PPMS) who were followed up for a median interval of 1.5 years. Balk et al. (2016) performed another study enrolling 135 MS patients (including 26 SPMS and 13 PPMS), who have been assessed with SD-OCT (Spectralis) over a 2-year period: the authors showed RNFL and GCIPL thinning to be significantly related to disease duration (with thinning rate becoming smaller in the presence of longer disease duration), and consistently, they found RNFL and GCIPL atrophy rate to be higher in RRMS than SPMS patients; such a relation was not identified for INL. Longitudinal data over 2 years relative to the cohort of 51 SPMS patients enrolled in the lipoic acid trial showed annualized RNFL and GCIPL atrophy rates (−0.31 and −0.29 μm/year, respectively) to not differ between eyes with and without previous ON history; however, a baseline RNFL thickness higher than 75 μm was associated with a greater (−0.85 μm/year) annualized atrophy rate (Winges et al., 2019). Only very recently Sotirchos et al. (2020) published a significant OCT longitudinal study including a cohort of 178 RMS and 186 PMS patients who were followed up with serial OCT scans (performed with Cirrus SD device) for a median of 3.7 years: independently from age, MS phenotype was found to be associated with faster mean annualized percent changes for both RNFL (−0.34%/year) and GCIPL (−0.27%/year), and possibly also for INL and ONL, with no significant impact determined by disease-modifying therapies; the relation between retinal layers atrophy rates and disability progression over time, however, has not been extensively assessed. Longitudinal OCT studies assessing evolution over time of retinal layers in PMS are summarized in Table 3.

**CONCLUDING REMARKS**

Optic pathway offers the unique opportunity to combine functional and structural measures: given the demonstrated correlations between optic nerve and brain damage (as revealed by MRI), it represents an attractive CNS area of interest to monitor MS evolution, as well as the response to DMTs, particularly in PMS. On the one hand, VEP studies, albeit in the presence of limited specific information, suggested a significant functional involvement of the visual pathway in PMS, in the presence of a relation with dynamic visual function measures and with a possible prognostic contribution on progression, in the context of a multimodal assessment of evoked responses. On the other hand, OCT studies, although in the presence of some contrasting results, highlighted a significant retinal neuro-axonal loss in PMS compared with HC but also RRMS patients, in the presence of possible, although non-linear, cross-sectional and longitudinal relations with measures of visual and global disability. Significant relations have been also identified in PMS between retinal neuro-axonal architecture and structural measures of brain atrophy provided by MRI; more recently, INL has been proposed as a marker of neuroinflammation also in the progressive phase of the disease. Our exploration of the literature, however, appears to highlight a lack of studies specifically combining a functional exploration of the visual pathway with a morphological description of the retina in PMS patients, with a still open possibility to better characterize the relation between demyelination and neurodegeneration in the progressive phase of the disease. To validate the use of VEPs and OCT in PMS, it is mandatory to recruit large cohorts of patients in the context of multicenter studies, longitudinally followed to define the correlations with clinically relevant visual parameters from the one side (i.e., contrast sensitivity measures) and with global disability measures on the other. Of great value could be also studies comparing combined OCT and VEPs data with conventional and advanced MRI techniques. A better knowledge in the field would be of fundamental importance in a near future, in order to identify the most suitable biomarkers to assess the efficacy of possible neuroprotective and remyelinating strategies aimed to contrast irreversible disability accrual affecting PMS patients.

**AUTHOR CONTRIBUTIONS**

All listed authors have made a substantial, direct and intellectual contribution to the present work, and approved it for publication. In particular, SG performed literature search and wrote the first draft of the manuscript. LL and GC completed bibliography and revised the manuscript.

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