# The use of optical coherence tomography and visual evoked potentials in the 2024 McDonald diagnostic criteria for multiple sclerosis

*Shiv Saidha, Ari J Green, Letizia Leocani, Angela Vidal-Jordana, Rachel C Kenney, Gabriel Bsteh, Olivier Outteryck, Alan Thompson, Xavier Montalban, Timothy Coetzee, Axel Petzold, Friedemann Paul, Laura J Balcer, Peter A Calabresi, on behalf of the International Multiple Sclerosis Visual System consortium**

*Lancet Neurol* 2025; 24: 880–92

This online publication has been corrected. The corrected version first appeared at thelancet.com/neurology on Sept 18, 2025

See **Position Paper** page 850 and **Personal View** page 866

*Members listed in the appendix (p 1)

**Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA** (Prof S Saidha MD, Prof P A Calabresi MD); **Weill Institute for Neurosciences, Department of Neurology, University of California, San Francisco, San Francisco, CA, USA** (Prof A J Green MD); **Department of Ophthalmology, University of California, San Francisco, San Francisco, CA, USA** (Prof A J Green); **Faculty of Medicine, University Vita-Salute San Raffaele, Milan, Italy** (Prof L Leocani MD); **Multiple Sclerosis Centre of Catalonia, Autonomous University of Barcelona, Barcelona, Spain** (A Vidal-Jordana PhD, Prof X Montalban PhD); **Department of Neurology, New York University School of Medicine, New York, NY, USA** (R C Kenney PhD, Prof L J Balcer MD); **Department of Population Health, New York University School of Medicine, New York, NY, USA** (R C Kenney, Prof L J Balcer); **Department of Neurology, Medical University of Vienna, Vienna, Austria** (Prof G Bsteh PhD); **Comprehensive Center for Clinical Neurosciences & Mental Health, Medical University of Vienna, Vienna, Austria** (Prof G Bsteh); **Department of Neuroradiology, U1172 Lil'NCOg, University of Lille, Lille, France** (O Outteryck MD); **Queen Square Multiple Sclerosis Centre, Department of Neuroinflammation, Queen Square Institute of Neurology,**

**The 2024 revisions of the McDonald diagnostic criteria include the optic nerve as a fifth anatomical location within the CNS for the diagnosis of multiple sclerosis, in addition to periventricular, juxtacortical or cortical, infratentorial, and spinal cord lesions. Demonstration of dissemination in space can now be achieved with the detection of typical lesions in at least two of these five locations. We review the evidence supporting the use of optical coherence tomography (OCT) and visual evoked potentials (VEPs) to show optic nerve involvement in the diagnosis of multiple sclerosis. We also report consensus recommendations for their use. Provided there is no better explanation for optic nerve involvement and that rigorous quality control is applied, OCT-derived peripapillary retinal nerve fibre layer inter-eye differences of 6 µm or greater or composite macular ganglion cell and inner plexiform layer inter-eye differences of 4 µm or greater support optic nerve injury. Delayed VEP latency, which depends on technical and methodological factors, and is centre and device dependent, supports demyelinating optic nerve injury when done with appropriate technical knowledge and interpretation.**

## Introduction

Multiple sclerosis is an immune-mediated demyelinating disorder of the CNS that frequently affects the sensory visual pathways, particularly the anterior visual pathway. Acute optic neuritis is the initial manifestation in approximately a quarter of people with multiple sclerosis and has been reported to occur in roughly half of patients at some point during their disease course.[1] Moreover, subclinical anterior visual pathway involvement is thought to be ubiquitous, and demyelinating plaques within the optic nerves are present post-mortem in almost all people with multiple sclerosis.[2,3] Despite this high frequency of involvement, the optic nerve has not been recognised as a lesion site in recent multiple sclerosis diagnostic criteria until 2024.[4,5]

The retinal nerve fibre layer (RNFL; the innermost layer of the retina) is comprised of unmyelinated axons that originate from retinal ganglion cells in the ganglion cell layer, immediately below the RNFL. The axons of the RNFL coalesce at the optic discs to form the optic nerves, exiting the sclera posteriorly via the lamina cribrosa, where they become myelinated by adjacent oligodendrocytes (figure 1). During periods of optic nerve inflammatory demyelination in multiple sclerosis, whether symptomatic or asymptomatic, some permanent injury to the optic nerve axons occurs. Such injury results in retrograde (ie, towards the retina), anterograde (ie, Wallerian), and possibly trans-synaptic axonal degeneration.[6–13] Surviving axons might still be susceptible to degeneration over time.[14–18] The net effect of retrograde degeneration of optic nerve axons is thinning of the RNFL and retinal ganglion cell death, which are reliably detectable by 3 months and mostly complete within 6 months of optic nerve inflammatory demyelination.[19–23] Post-mortem studies reveal retinal ganglion cell loss in approximately 80% of eyes of people with multiple sclerosis.[7,24] Optic neuritis causes inflammation, demyelination, and neurodegeneration in the visual pathways of people with multiple sclerosis. Acute optic neuritis is characterised by subacute vision loss, reduced visual acuity, impaired colour vision, and a relative afferent pupillary defect in the affected eye. Typical optic neuritis in people with multiple sclerosis is usually unilateral, with generally only mild optic disc swelling, differing from myelin oligodendrocyte glycoprotein-associated disease (MOGAD)-related and neuromyelitis optica spectrum disorder (NMOSD)-related optic neuritis.

Optical coherence tomography (OCT) and visual evoked potentials (VEPs) are reliable paraclinical tests to identify both acute and previous optic nerve injury associated with multiple sclerosis. To complement the 2024 revisions of the McDonald criteria by Montalban and colleagues,[25] in this Personal View, we review the principal OCT and VEP evidence supporting the addition of the optic nerve as a fifth anatomical location within the CNS to the dissemination in space criteria. We also provide practical guidance for using OCT and VEPs in clinical practice and recommendations for the clinical interpretation of the parameters derived from these tests, emphasising that these tests primarily serve as adjuncts to careful and thorough clinical assessments.

## Methods

In December 2023, a consensus conference—convened by the International Advisory Committee on Clinical Trials in Multiple Sclerosis and sponsored by the European Committee for Treatment and Research in Multiple Sclerosis and the US National Multiple Sclerosis Society—considered data-driven propositions to update the 2017 McDonald diagnostic criteria.[5,25,26] The committee voted

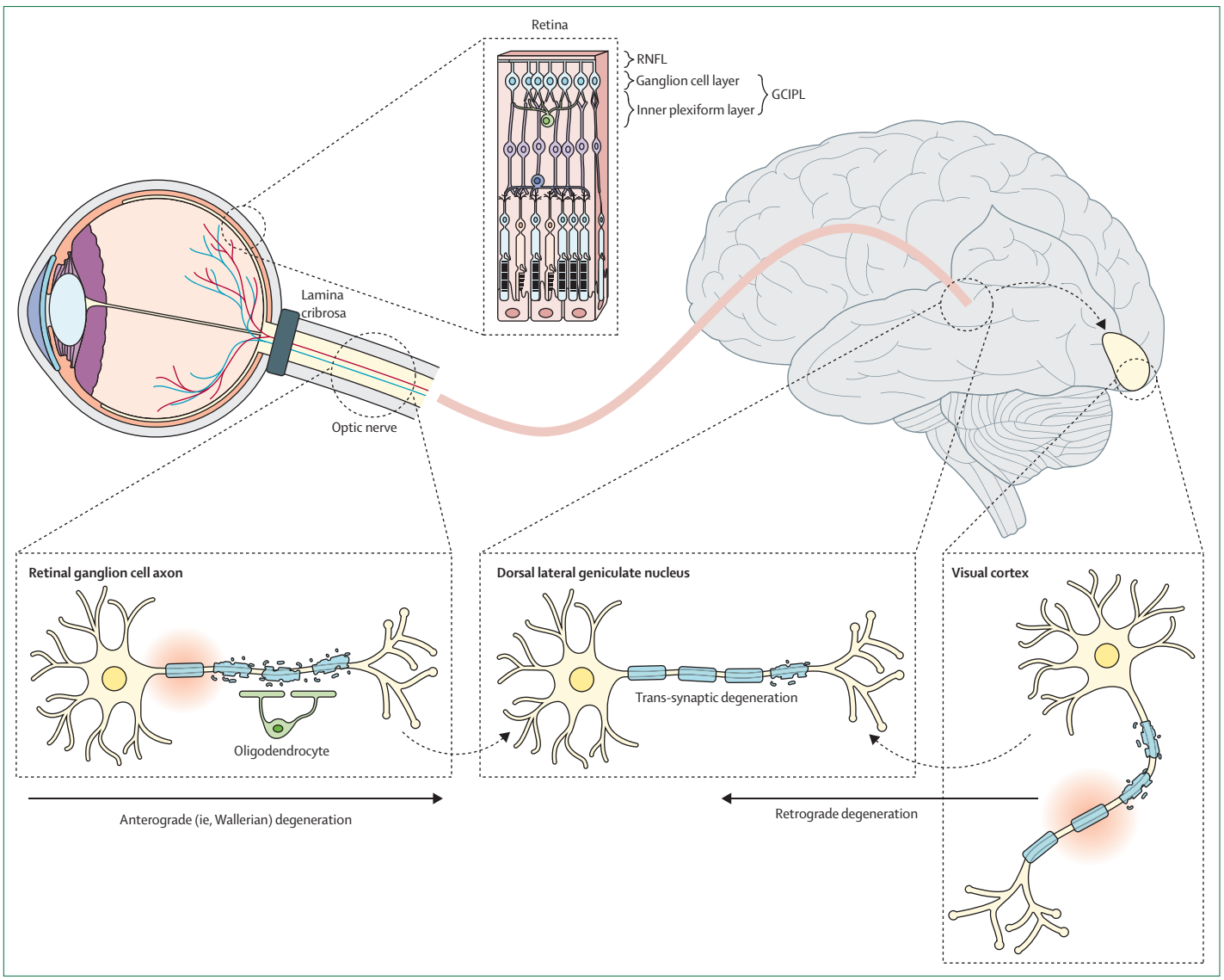



***Figure 1:*** **Basic anatomy of the visual system and mechanisms underlying retinal neurodegeneration**
The RNFL consists of unmyelinated axons originating from retinal ganglion cells located in the ganglion cell layer. For technical reasons, the ganglion cell layer is often combined with the inner plexiform layer, which is situated immediately below the ganglion cell layer and primarily contains synapses between bipolar cells (which transmit signals from retinal photoreceptors) and retinal ganglion cells. The axons in the RNFL converge at the optic disc to form the optic nerve, exiting the sclera posteriorly through the lamina cribrosa, from where they are myelinated by adjacent oligodendrocytes. During episodes of inflammatory demyelination of the optic nerve, whether symptomatic or asymptomatic, permanent injury to the affected optic nerve axons typically occurs. This injury results in retrograde (ie, toward the retina), anterograde (ie, Wallerian), and trans-synaptic axonal degeneration. RNFL=retinal nerve fibre layer. GCIPL=ganglion cell and inner plexiform layer.

unanimously to include the optic nerve as a fifth distinct anatomical location for meeting dissemination in space criteria for relapsing-onset and progressive-onset multiple sclerosis.[25] Furthermore, it was recognised that there is ample evidence to support the clinical use of OCT, VEPs, and optic nerve MRI to objectively identify optic nerve involvement for the diagnosis of multiple sclerosis.

## OCT and VEPs

OCT is a rapid, well tolerated, easily repeatable, reproducible, relatively inexpensive, and non-invasive imaging technique that uses near-infrared light to generate cross-sectional or three-dimensional (3D) images of tissues such as the retina.[27,28] Current, commercially available spectral-domain OCT imaging has approximately 3–5 µm axial resolution—substantially greater than that of conventional MRI. This high resolution enables assessment of the retina, including quantification of the peripapillary retinal nerve fibre layer (pRNFL) thickness, which measures around 90–110 µm on average in the eyes of controls. Macular segmentation techniques can also be applied to objectively and precisely quantify discrete retinal layers using OCT, including the composite of the macular

**Faculty of Brain Sciences, University College London, London, UK** (Prof A Thompson MD); **Department of Neurology, Vall d'Hebron University Hospital, Autonomous University of Barcelona, Barcelona, Spain** (Prof X Montalban); **Universitat de Vic–Central de Catalunya, Vic, Spain** (Prof X Montalban); **National Multiple Sclerosis Society, New York, NY, USA** (T Coetzee PhD); **Queen Square**

**Institute of Neurology, Faculty of Brain Sciences, University College London, London, UK** (Prof A Petzold PhD); **Department of Neuro-ophthalmology, National Hospital for Neurology and Neurosurgery and Moorfields Eye Hospital, London, UK** (Prof A Petzold); **NeuroCure Clinical Research Center, Charité, Department of Neurology, Experimental and Clinical Research Center, Max Delbrueck Center for Molecular Medicine, and Charité Universitätsmedizin Berlin, Berlin, Germany** (Prof F Paul MD); **Department of Ophthalmology, New York University School of Medicine, New York, NY, USA** (Prof L Balcer); **Wilmer Eye Institute, Department of Ophthalmology, Johns Hopkins University School of Medicine, Baltimore, MD, USA** (Prof P A Calabresi); **Solomon Snyder Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD, USA** (Prof P A Calabresi)

Correspondence to:
Prof Shiv Saidha, Department of Neurology, Johns Hopkins School of Medicine, Baltimore, MD 21287, USA
**ssaidha2@jhmi.edu**

or

Prof Peter A Calabresi, Department of Neurology, Johns Hopkins School of Medicine, Baltimore, MD 21287, USA
**pcalabr1@jhmi.edu**

See Online for appendix

For more on the **International Multiple Sclerosis Visual System (IMSVISUAL) Consortium** see www.imsvisual.org

ganglion cell and inner plexiform layer (GCIPL). GCIPL thickness measures might have several advantages over conventional pRNFL thickness measures, including superior reproducibility, reliability, and structure–function relationships with visual function, visual quality-of-life, and global disability scores.[29–35] In reproducibility and reliability studies, the intervisit intraclass correlation coefficient for GCIPL thickness was found to be extremely high (~0·98/0·99), and although the intervisit intraclass correlation coefficient for pRNFL thickness was only slightly lower, the coefficient of variation and test-retest standard deviation for GCIPL thickness has been found to be generally superior to those for pRNFL thickness, including in multicentre studies.[36,37] OCT is already included as a paraclinical test in consensus diagnostic criteria for optic neuritis and has performed well in validation studies of these diagnostic criteria.[38–41]

VEPs allow for the measurement of the electrical conduction from the retina through the visual pathways to the occipital visual cortices. VEP latency provides a functional measurement of myelin integrity in the visual pathways, as conduction velocity is principally dependent on myelin-mediated saltatory conduction.[42–44] The most validated and standard technique used in clinical practice is full-field, checkerboard, pattern-reversal VEPs, which has an excellent intervisit intraclass correlation coefficient of VEP latency of approximately 0·90.[45] The waveform peak potential observed at around 100 ms (referred to hereafter as P100) is the most prominent and reproducible VEP waveform. P100 latency might not solely reflect the time from retinal stimulation to occipital cortical response but might also reflect contributory time for signal responses to return from the accessory visual areas.[43,44,46] VEP latency delays can detect functional abnormalities in the visual pathways that correlate with optic nerve injury, even when asymptomatic. VEP latency delay correlates with optic nerve lesion length on MRI in people with multiple sclerosis and with the extent of myelin damage in animal models of demyelination.[44,47–49] However, an important limitation of measuring VEP latency delay, particularly when mild, is that it is not optic nerve-specific. Delays can also be detected in certain retinal disorders, especially those involving the macula, and in refractive abnormalities such as severe myopia. Therefore, VEP latency delays should be carefully considered within the clinical context.

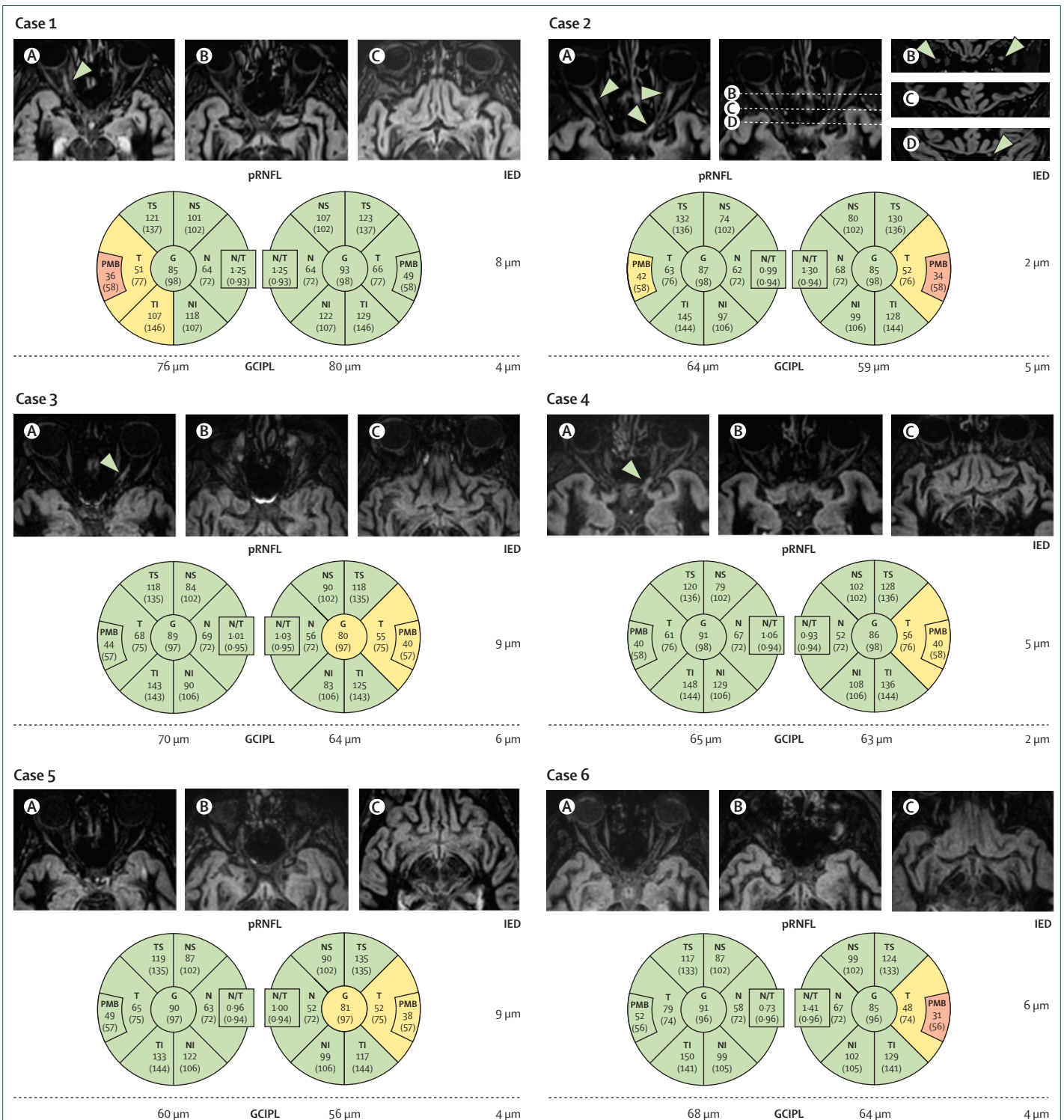
OCT imaging of the optic nerve head and macula might help inform VEP assessments, and vice versa, highlighting their complementary roles in clinical practice. Unlike optic nerve MRI and OCT, which might show distinct patterns that help differentiate NMOSD-related or MOGAD-related optic neuritis, mild VEP abnormalities might be of less value for differential diagnosis. Caution should be exercised when using any of the techniques for visual assessment in isolation. In a similar manner to using MRI as a paraclinical tool, OCT and VEPs are paraclinical tests to support the diagnosis of multiple sclerosis that require decision making within the clinical context.

## Evidence supporting the use of OCT and VEPs in multiple sclerosis diagnosis

### Detection of optic nerve involvement

A systematic literature review and meta-analysis done by the International Multiple Sclerosis Visual System (IMSVISUAL) Consortium included OCT scans of 5776 eyes from people with multiple sclerosis (1667 eyes with known previous optic neuritis and 4109 eyes without a known history of optic neuritis), as well as 1697 eyes of healthy controls from 40 studies.[50,51] Among eyes from healthy controls, the average pRNFL thickness was 104·4 µm and the average GCIPL thickness was 70·03 µm. Relative to the eyes of healthy controls, the average pRNFL thickness in the eyes of people with multiple sclerosis with a known previous history of clinical optic neuritis was 20·1 µm lower, and the average pRNFL thickness was 7·41 µm lower in the eyes of those without an identified clinical history of previous optic neuritis. Similarly, compared with the eyes of healthy controls, the average GCIPL thickness was 16·42 µm lower in the eyes of individuals with multiple sclerosis with a known previous history of optic neuritis, and was 7·75 µm lower in those without a known previous history of optic neuritis. The findings of this meta-analysis show that average pRNFL and GCIPL thicknesses are reduced in the eyes of people with multiple sclerosis, both with and without a known history of optic neuritis, and as expected, to a greater extent in the eyes of those patients with a previous history of optic neuritis (appendix pp 3–4).

The differences in pRNFL and GCIPL thicknesses between the eyes of people with multiple sclerosis and eyes of healthy controls has stimulated investigation to identify the role of inter-eye differences for documenting optic nerve involvement for dissemination in space (appendix p 7).[52,53] An international, multicentre study included 368 healthy controls, 854 people with multiple sclerosis without an identified history of previous optic neuritis, and 477 people with multiple sclerosis with a history of previous unilateral optic neuritis (appendix pp 4–5).[52] The optimal inter-eye difference threshold for identifying people with multiple sclerosis with previous unilateral optic neuritis was 5 µm (area under the curve [AUC] 0·74) for the pRNFL and 4 µm (AUC 0·77) for the GCIPL across OCT devices. However, the optimal pRNFL inter-eye difference threshold was slightly different between the two predominant OCT devices used in the study: 5 µm on Spectralis (Heidelberg Engineering, Heidelberg, Germany) and 6 µm on Cirrus HD-OCT (Carl Zeiss, Dublin, CA, USA); whereas the optimal GCIPL inter-eye difference thresholds were practically the same for both devices (approximately 4 µm). These two OCT devices were found to reflect the majority of OCT devices in use




(Figure 2 continues on next page)

across numerous international sites in a previous IMSVISUAL survey.[51] We provide recommendations of scanning protocols for both devices in the appendix (pp 8–11). VEPs are especially sensitive for identifying optic nerve lesions in the acute phase of optic neuritis, as P100 latency delay often improves over time following

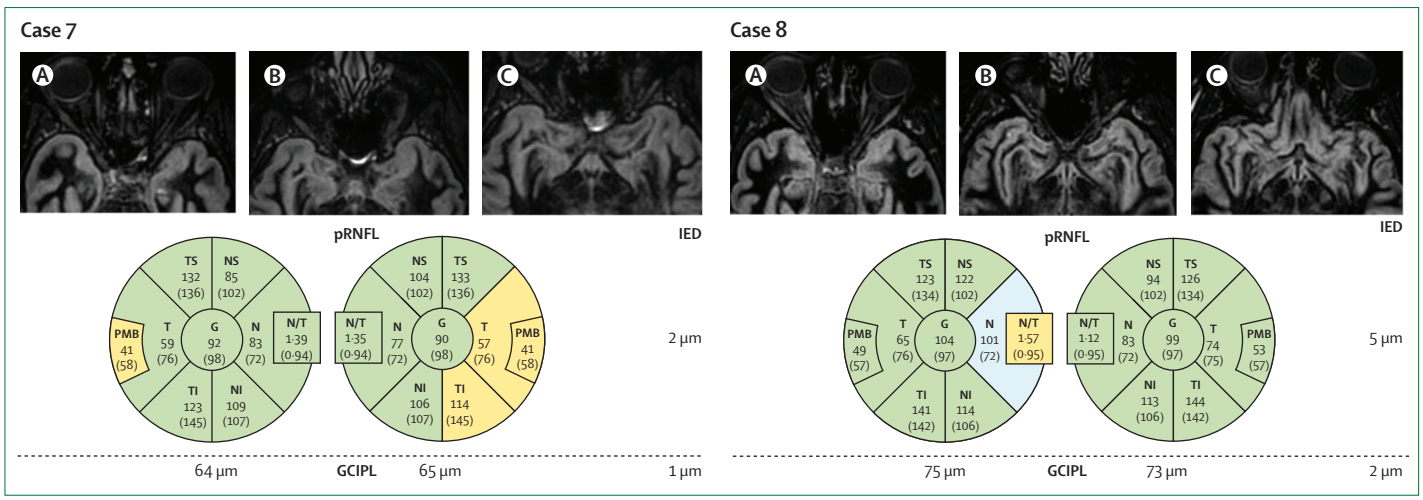



***Figure 2:*** **Optic nerve lesions detected by OCT and matching optic nerve MRI**

This figure describes eight different cases of people presenting within 6 months of onset of clinically isolated syndrome, which is suggestive of multiple sclerosis. Peripapillary and macular OCT (Spectralis) scans were done at the same time as a brain MRI that included a three-dimensional double-inversion recovery sequence (fluid and fat suppressed). In case 1 and cases 3–8, three axial MRI reconstructions are presented, focusing on the optic nerves (A), optic chiasm (B), and optic tracts (C). In case 2, an axial MRI reconstruction of the optic nerve is shown (A), as well as coronal slices (B–D) focusing on the optic nerves. No lesions were identified in the optic chiasms or optic tracts in any of these cases. The pRNFL thickness maps are derived from the OCT reports with the absolute IED of pRNFL and macular GCIPL thicknesses provided for each patient. In the pRNFL OCT reports, red represents values in the <1st percentile, yellow represents values in the <5th percentile, green represents values between the 5th and 95th percentiles, and blue represent values in the >95th percentile versus age-matched healthy controls. Each patient subsequently went on to develop clinically definite multiple sclerosis during follow-up. Case 1: patient who presented with a first episode of right-sided acute optic neuritis 6 months previously. On MRI, a symptomatic right-sided optic nerve lesion within the orbital region (arrowhead) was observed. pRNFL and GCIPL IEDs were above the proposed thresholds and confirm right-sided optic nerve involvement (lower pRNFL and GCIPL thicknesses in the right eye *vs* the left eye). Case 2: patient who presented with a first episode of transverse myelitis 3 months before these assessments. MRI shows bilateral asymptomatic optic nerve lesions, with at least two discrete lesions evident within the left optic nerve (arrowheads; orbital section of the right optic nerve, and orbital and canalicular sections of the left optic nerve). Coronal slices (B–D) confirmed the optic nerve lesions. Only the IED of the GCIPL was considered abnormal, with the GCIPL thickness being lower in the left eye than the right eye. Case 3: patient who presented with an episode of acute myelitis 3 months before these assessments. MRI highlighted a left asymptomatic optic nerve lesion (arrowhead). pRNFL and GCIPL IEDs were above the proposed thresholds, with both pRNFL and GCIPL thickness measures lower in the left eye than the right eye, confirming the presence of a left-sided optic nerve lesion. Case 4: patient who presented with a first episode of myelitis approximately 3 months before these assessments. pRNFL and GCIPL IEDs were below the proposed thresholds for optic nerve involvement. Only MRI detected an asymptomatic left-sided optic nerve lesion within the canalicular part (arrowhead). This case illustrates that not all visible optic nerve lesions on MRI are associated with IEDs in pRNFL or GCIPL thickness measures that meet the proposed thresholds for defining optic nerve involvement. Case 5: patient who presented with an episode of myelitis about 3 months before these assessments. No optic nerve lesions were visible on optic nerve MRI. pRNFL and GCIPL IEDs were above the proposed thresholds, with both pRNFL and GCIPL thickness measures lower in the left eye than the right eye, confirming the presence of a left-sided optic nerve lesion. Left temporal pRNFL atrophy is shown. This case illustrates that optic nerve MRI does not always show visible optic nerve lesions, even when the OCT is abnormal and supportive of optic nerve involvement, underpinning the complementary role of paraclinical tools for identifying optic nerve involvement. Case 6: patient who presented with a first acute episode of myelitis 6 months before these assessments. No optic nerve lesion was detected on MRI. pRNFL and GCIPL IEDs were above the proposed thresholds, with both pRNFL and GCIPL thickness measures lower in the left eye than the right eye, confirming the presence of a left-sided optic nerve lesion. Furthermore, a left-sided temporal pRNFL thickness reduction is also evident. Case 7: patient who presented with a symptomatic tumefactive demyelinating brain lesion 3 months before these assessments. No optic nerve lesion was detected by MRI or OCT. IEDs remain below the proposed thresholds. No optic nerve lesion was detected. Case 8: patient who presented with a first episode of acute myelitis about 3 months before these assessments. No optic nerve lesion was detected by MRI or OCT. IEDs remain below the proposed thresholds. There is no evidence of optic nerve involvement. In the examples above, particularly in cases for whom OCT and MRI are negative, it should be noted that visual evoked potentials might also have a complementary role in the identification of optic nerve involvement. OCT=optical coherence tomography. pRNFL=peripapillary retinal nerve fibre layer. IED=inter-eye difference. TS=superior-temporal sector. NS=superior-nasal sector. PMB=papillomacular bundle. T=temporal sector. G=global average pRNFL thickness. N=nasal sector. N/T=nasal-temporal ratio. TI=inferior-temporal sector. NI=inferior nasal sector. GCIPL=ganglion cell and inner plexiform layer.

acute optic neuritis, particularly in younger patients, most likely due to endogenous remyelination.[42,54,55] In longitudinal studies, VEP P100 latency delays were detected in 77–100% of symptomatic eyes during the acute phase and in 62·2–80% of eyes after 12–24 months, indicating some degree of functional recovery.[56,57] Studies that have assessed VEPs in cohorts with clinically isolated syndrome—an initial clinical presentation suggestive of multiple sclerosis—report abnormal VEPs in 15–49% of patients.[58–61] VEP abnormalities were more common among patients with clinically isolated syndrome with optic neuritis (66·7–87%) versus those with non-optic neuritis presentations (13·6–22·5%).[62–64] These findings emphasise the utility of VEPs in confirming previous optic neuritis, albeit potentially less useful than for confirming optic neuritis during its acute phase.

## Detection of asymptomatic optic nerve lesions

For OCT and VEPs to be useful in the diagnosis of multiple sclerosis, they should detect asymptomatic optic nerve involvement with specificity. A study by Nolan-Kenney and colleagues[52] ascertained that 45% of participants with multiple sclerosis with inter-eye differences in pRNFL thickness and 34% of those with inter-eye differences in GCIPL thickness above the predefined thresholds of 5 µm (pRNFL) and 4 µm (GCIPL) did not have a previous history of optic neuritis. Although these observations do not definitively confirm optic nerve involvement, these participants also had differences in low-contrast visual acuity scores between eyes, which suggests functional implications that might be clinically relevant.

In another study of 98 people with multiple sclerosis that used 3D double-inversion recovery MRI sequences

of the optic nerve—a technique used primarily in research—and OCT, 54% (n=53) of these participants had a history of optic neuritis.[65] In many, but not all asymptomatic eyes, optic nerve hyperintensites (ie, lesions) were visible on MRI. Symptomatic MRI optic nerve lesions were associated with the greatest reductions in pRNFL and GCIPL thicknesses measured by OCT and in low-contrast visual acuity. Asymptomatic MRI optic nerve lesions were also associated with lower values of these measures than the values obtained in eyes without visible MRI lesions. These findings suggest that asymptomatic optic nerve involvement might be associated with functionally relevant structural changes that can be detected by OCT (figure 2). Outteryck and colleagues[66] conducted OCT and 3D double-inversion recovery MRI in another cohort of 130 people within 4·5 months of clinically isolated syndrome presentation. In those presenting with acute optic neuritis, MRI lesions were detected in all symptomatic optic nerves, suggesting that MRI has greater sensitivity to detect symptomatic optic nerve lesions the closer it is done to the clinical event itself. People with asymptomatic optic nerve lesions on MRI had greater inter-eye differences in pRNFL and GCIPL thicknesses versus people without optic nerve lesions on MRI, albeit comparatively lower than the inter-eye differences for eyes with symptomatic optic nerve lesions. In this study, within patients without optic neuritis, the pRNFL and GCIPL inter-eye difference thresholds (5 μm for pRNFL and 4 μm for GCIPL [based on Spectralis results], which were defined in Nolan-Kenney and colleagues' study for identifying the eyes of people with multiple sclerosis with previous optic neuritis)[52] had low sensitivities (48·3% for pRNFL; 25% for GCIPL), but extremely high specificities (88·7% for pRNFL; 98·4% for GCIPL) for identifying asymptomatic optic nerve lesions. These high specificities suggest that exceeding such pRNFL and GCIPL inter-eye difference thresholds is very likely to reflect pathological optic nerve involvement, which could suggest dissemination in space. Of note, asymptomatic optic nerve lesions detected with MRI are rarely seen in NMOSD or MOGAD.[67,68] A noteworthy limitation of the 3D double-inversion recovery studies is that this imaging of the optic nerve is not routinely available and is not recommended in the 2024 McDonald criteria.

There is longstanding evidence showing that VEPs can identify asymptomatic optic nerve lesions in multiple sclerosis. Some studies indicated a greater likelihood of detecting clinically silent lesions with VEPs than with brainstem-auditory and somatosensory evoked potentials.[69,70] Furthermore, multiple studies also established that P100 latency delay on VEP predicted conversion from clinically probable to clinically definite multiple sclerosis under the previously used Poser diagnostic criteria.[59,71,72] People without a previous history of optic neuritis might also have VEP latency delays, albeit relatively mild. Such delays should be assessed together with potential functional deficits, OCT changes suggesting optic nerve involvement, and MRI changes suggestive of demyelinating optic nerve injury. The frequency of detecting VEP P100 latency delays is influenced by the disease course, and detection is more common in more advanced disease than in clinically isolated syndrome, for example.[73] Furthermore, VEPs and OCT might be useful for showing optic nerve involvement in primary progressive multiple sclerosis, in which they are also frequently abnormal.[74]

### Diagnostic performance when adding optic nerve involvement

Before the inclusion of the optic nerve in the 2024 revisions of the McDonald criteria for the diagnosis of multiple sclerosis as the fifth anatomical location for dissemination in space, three studies investigated the effect on diagnostic accuracy of modifying the dissemination criteria of the 2017 McDonald diagnostic criteria to include the optic nerve (table 1).[63,64,75]

Bsteh and colleagues[75] included 267 people with a first demyelinating event in whom dissemination in space was assessed 180 days or less from first symptom onset. Optic nerve involvement was assessed by OCT (inter-eye differences in pRNFL thickness of ≥5 μm or GCIPL thickness of ≥4 μm). The primary endpoint of the study was time to a relapse after a median follow-up of 59 (13–98) months. As the number of anatomical locations affected increased, so too did the risk of a clinical attack. In people fulfilling the modified 2017 dissemination in space criteria (ie, two or more of five regions affected, including the optic nerve), the risk for a second clinical attack was slightly higher (although the risk was deemed overall similar due to the overlap in CIs) compared with the risk in people fulfilling the unmodified 2017 criteria (ie, two or more of the four regions affected, not including the optic nerve). However, this analysis included participants with relatively short periods of follow-up, and therefore there were fewer opportunities for clinical events to occur. In the subgroup of people with at least 5 years of follow-up (n=118), the modified 2017 criteria improved diagnostic accuracy from 65·6% to 81·2%, together with a modest increase in sensitivity and no change in specificity. Furthermore, the modified 2017 criteria performed similarly in people in whom their first demyelinating event was an acute optic neuritis or a non-optic neuritis event.

Vidal-Jordana and colleagues[63] evaluated the modified 2017 dissemination in space criteria that include the optic nerve in a retrospective study of 151 people with multiple sclerosis with at least 10 years of follow-up. Optic nerve involvement was assessed by VEPs. The primary outcome was the occurrence of a relapse. The accuracy of diagnosis increased from 75·5% to 78·1%, sensitivity increased from 79·2% to 82·3%, and specificity remained similar when using the modified 2017 dissemination in

| | Sensitivity (95% CI) | Specificity (95% CI) | Positive predictive value (95% CI) | Negative predictive value (95% CI) | Accuracy (95% CI) |
|---|---|---|---|---|---|
| **Optic nerve assessment by VEPs*** | | | | | |
| DIS 2017† | 79·2 (71·2–85·8) | 52·4 (29·8–74·3) | 75·5 (67·8–82·1) | 91·1 (86·7–94·2) | 28·9 (19·4–40·9) |
| Modified DIS (VEP)‡ | 82·3 (74·6–88·4) | 52·4 (29·8–74·3) | 78·1 (70·7–84·5) | 91·4 (87·1–94·4) | 32·3 (21·6–45·4) |
| **Optic nerve assessment by OCT§** | | | | | |
| DIS 2017† | 77·9 (68·6–85·1) | 52·2 (33·0–70·8) | 87·1 (78·3–92·6) | 36·4 (22·2–53·4) | 65·6 (52·3–78·8) |
| Modified DIS (OCT)‡ | 84·2 (75·6–90·2) | 52·2 (33·0–70·8) | 87·9 (79·6–93·1) | 44·4 (27·6–62·7) | 81·2 (70·6–91·9) |
| **Optic nerve assessment by either MRI, OCT, or VEPs¶** | | | | | |
| DIS 2017† | 88·2 (80·6–93·6) | 82·2 (67·9–92·0) | 86·5 (80·0–91·4) | 92·4 (86·6–95·8) | 74·0 (62·7–82·8) |
| Modified DIS (MRI)‡ | 92·5 (84·4–97·2) | 71·9 (53·3–86·3) | 86·6 (78·9–92·3) | 89·2 (82·5–93·5) | 79·3 (63·3–89·5) |
| Modified DIS (OCT-pRNFL)‡ | 91·0 (83·1–96·0) | 74·3 (56·7–87·5) | 86·3 (79·0–91·8) | 90·0 (83·6–94·1) | 76·5 (62·0–86·6) |
| Modified DIS (OCT-GCIPL)‡ | 91·4 (83·0–96·5) | 80·0 (61·4–92·3) | 88·3 (80·8–93·6) | 92·5 (85·7–96·2) | 77·4 (62·3–87·7) |
| Modified DIS (VEP)‡ | 89·9 (81·7–95·3) | 78·1 (62·4–89·4) | 86·2 (79·0–91·6) | 89·9 (83·3–94·1) | 78·1 (65·2–87·1) |
| Modified DIS (any test) | 91·8 (85·0–96·2) | 71·1 (55·7–83·6) | 85·8 (79·3–90·9) | 88·6 (83·0–93·5) | 78·1 (64·2–87·2) |

DIS=dissemination in space. VEP=visual evoked potentials. OCT=optical coherence tomography. pRNFL=peripapillary retinal nerve fibre layer. GCIPL=ganglion cell and inner plexiform layer. *Vidal-Jordana et al (2021): a retrospective study (N=388) with the outcome of clinically definite multiple sclerosis.[63] †DIS criteria as defined in 2017 McDonald criteria: at least one lesion in two or more of the four regions (periventricular, cortical or juxtacortical, infratentorial, and spinal cord).[5] ‡Modified DIS criteria (DIS and optic nerve involvement by each technique detailed) were constructed by adding the optic nerve region (defined by either abnormal VEPs, abnormal inter-eye differences in OCT measures, or MRI, as specified): at least one lesion in two or more of the five regions (periventricular, cortical or juxtacortical, infratentorial, spinal cord, and optic nerve). §Bsteh et al (2023): a retrospective study (N=267) with the outcome of clinically definite multiple sclerosis.[75] ¶Vidal-Jordana et al (2024): a prospective study (N=157) with the 2017 McDonald multiple sclerosis criteria as the outcome.[64]

***Table 1:*** **Diagnostic performance of DIS criteria with and without optic nerve assessment**

space criteria relative to the unmodified criteria. Vidal-Jordana and colleagues[64] also conducted a longitudinal, prospective study across five multiple sclerosis centres from the MAGNIMS network, including 157 people with clinically isolated syndrome, with the primary outcome being multiple sclerosis diagnosis with the 2017 McDonald criteria. Participants underwent optic nerve assessments within 6 months of symptom onset using optic nerve MRI, OCT, and VEPs. The diagnostic performance of the modified 2017 dissemination in space criteria varied depending on the paraclinical test used (table 1). Overall, compared with the unmodified criteria, including the optic nerve in the modified criteria resulted in an increase in sensitivity, with a slight decrease in specificity. This decrease in specificity was attributed to the relatively short follow-up period of approximately 3 years, the initiation of treatment during the study, and because the unmodified criteria were embedded in the primary outcome.

The high diagnostic performance of the modified dissemination in space criteria in these studies might have resulted from the high quality control of OCT, the exclusion of participants with potentially confounding ocular conditions and other comorbidities, as well as the enrolment of people with clinically isolated syndrome at high risk for developing multiple sclerosis, which might limit the generalisability of the findings. The enrolment of those with clinically isolated syndrome might not be representative of people with possible multiple sclerosis presenting with vague symptoms and non-specific white matter abnormalities on brain MRI. In these situations, the performance or added benefit of OCT or VEPs in the diagnosis of multiple sclerosis remains unknown. Moreover, the studies that supported the inclusion of the optic nerve in the diagnostic criteria were conducted in adults. The performance of these tests in children—in whom other conditions such as MOGAD are more prevalent than in adults—remains to be explored.

## Consensus recommendations for using OCT or VEPs to detect optic nerve involvement in multiple sclerosis

In the 2024 revisions of the McDonald criteria for the diagnosis of multiple sclerosis, the optic nerve is added to the four previously designated dissemination in space anatomical locations: the periventricular, juxtacortical or cortical, infratentorial, and spinal cord locations. Dissemination in space criteria for multiple sclerosis diagnosis can now be met with the involvement of two or more of these five locations (panel).[25,26]

Provided there is no better explanation for optic nerve injury or the patient's neurological presentation, and rigorous quality control is applied, we recommend use of a pRNFL inter-eye difference of 6 µm or greater and a composite macular GCIPL inter-eye difference of 4 µm or greater to support the presence of an optic nerve lesion detected by OCT. These recommendations approximate or exceed the 95th percentile for inter-eye differences in healthy controls, regardless of OCT device.

VEP P100 latency delay or asymmetric interocular VEP latencies (2·5 SD above the mean in both cases) might similarly support the presence of demyelinating optic nerve injury. However, the exact measures depend on technical and methodological factors, and are also centre

and device dependent. Individual VEP measures should be compared against normative values established at each centre (appendix p 4). Stringent VEP criteria are necessary to reduce false-positive readings, sacrificing sensitivity for specificity, which is appropriate in the diagnostic criteria of a lifelong disease. Caution should be exercised when interpreting bilateral VEP delays, particularly when associated with abnormal morphology, since both pre-chiasmal and retro-chiasmal lesions can contribute to bilateral VEP abnormalities.[46]

Optic nerve MRI with fat saturation can better highlight symptomatic and asymptomatic T2-hyperintense optic nerve lesions than conventional brain MRI.[38] Therefore, optic nerve MRI could be included as part of the diagnostic investigation of multiple sclerosis, and might also help differentiate optic neuritis caused by multiple sclerosis from other causes of optic neuritis (eg, MOGAD and NMOSD) and optic neuropathies. Further details regarding optic nerve MRI are discussed separately in the MRI companion paper to the 2024 revisions of the McDonald diagnostic criteria.[26]

## Important considerations for the use of OCT and VEPs

Several factors could limit the reliability of using OCT and VEPs as paraclinical tests in the diagnosis of multiple sclerosis (concurrent ophthalmological disorders, improper quality control, differential diagnoses, etc). Concurrent ophthalmological disorders, including amblyopia, glaucoma, compressive optic neuropathy, and congenital deficits, can affect OCT measures. We recommend a careful evaluation of patterns of injury in such contexts. Outer retinal disorders (eg, age-related macular degeneration), substantial uncorrected refractive errors, and untreated cataracts might affect VEP latency and should be appropriately evaluated.

Optic neuropathy can be caused by other inflammatory causes (eg, MOGAD and NMOSD), as well as infectious, vascular, metabolic, nutritional, drug-induced, genetic, and toxic causes.[38,76,77] The use of OCT, VEPs, and optic nerve MRI for showing optic nerve involvement in suspected multiple sclerosis should therefore be firmly grounded within the appropriate clinical context to minimise the risk of misdiagnosis.

Furthermore, high myopia (>6 diopters) can cause pRNFL and GCIPL thinning, although in these cases, different patterns of pRNFL thinning tend to be observed, such as a superior-inferior predominant pattern in myopia and a temporal predominant pattern in multiple sclerosis (appendix pp 12–15).[78] Similarly, anisometropia might cause apparent inter-eye differences.[79] Assessing the GCIPL thickness maps for patterns of regional macular injury might provide insight into the vascular causes of optic neuropathy, such as when altitudinal thinning is present, or when optic chiasm, optic tract, thalamic, and retrogeniculate pathology might be present.[80–83] The degrees of pRNFL and GCIPL thinning might also be informative, as people with NMOSD and MOGAD with a previous history of optic neuritis often have lower pRNFL and GCIPL thicknesses than people with multiple sclerosis who have previous optic neuritis (appendix pp 12–15).[84–87] Similarly, the degree of pRNFL swelling during the acute phase of optic neuritis tends to be higher in MOGAD than multiple sclerosis.[88] Comorbidities (poorly controlled hypertension, diabetes, etc) can also affect OCT measures. Petzold and colleagues[89] found that the multiple sclerosis diagnostic accuracy of inter-eye differences in OCT measures diminished according to the number and classes of comorbidities present, highlighting the importance of interpreting OCT within the context of comorbidities.

Quality control considerations are paramount for the reliable use of OCT and VEPs.[46,90–94] A review process of acquired OCT images is necessary to ensure that the retinal layer thickness measurements are accurate, thereby minimising false-positive and false-negative

***Panel:*** **OCT and VEPs to detect optic nerve involvement: definitions and practical considerations**

**Definition of optic nerve lesion**

- By use of OCT: inter-eye differences in pRNFL thickness of 6 µm or greater, or GCIPL thickness of 4 µm or greater
- By use of VEPs: delayed latency or interocular asymmetry in VEP latencies (based on normative data specific to the centre where the test is done)

**Considerations when interpreting OCT and VEP results**

- Rule out concurrent ophthalmological disorders and substantial refractive errors, as these might affect both OCT and VEP results*
- Review patient comorbidities, especially uncontrolled hypertension and diabetes, which can affect OCT-derived measures
- Ensure OCT and VEPs adhere to international quality control guidelines
- Note that OCT and VEP findings are not disease-specific; define optic nerve lesions after ruling out other possible explanations for OCT and VEP findings

**Considerations when selecting OCT or VEPs: time elapsed since acute optic neuritis**

- VEPs are more sensitive in the acute phase of optic neuritis relative to chronic optic neuropathy, as latency often improves over time following optic neuritis due to remyelination
- OCT-defined inter-eye differences have been validated for use 3 months or more after unilateral acute optic neuritis; note that OCT has not yet been validated for detecting bilateral optic nerve involvement for aiding the diagnosis of multiple sclerosis

OCT=optical coherence tomography. VEP=visual evoked potential. pRNFL=peripapillary retinal nerve fibre layer. GCIPL=ganglion cell and inner plexiform layer. *For VEPs, ensure testing is done with appropriate refractive correction.

| | Description | Criteria and thresholds | Application |
|---|---|---|---|
| OSCAR-IB | Established quality control protocol for OCT images | Includes: O (obvious problems), S (signal strength), C (scan centration), A (algorithm failure), R (retinal pathology), I (illumination uniformity), and B (beam placement) | Assesses overall quality and artifacts; widely used in clinical and research settings |
| Signal quality | Metric for image clarity and signal quality | Acceptable threshold varies by device (eg, signal strength of ≥7 for Cirrus HD-OCT or a quality score of ≥15 for Spectralis) | Ensures adequate signal quality for reliable interpretation |
| Artifacts check | Identifies artifacts (eg, floaters, blinking, and motion) | Minimal to no artifacts for optimal image | Enhances diagnostic accuracy by minimising errors caused by image artifacts |
| Scan depth and focus | Proper depth and focus alignment in OCT | Focused fundus image on retinal vasculature | Ensures retinal layer structures are correctly represented |
| Image centration | Ensures images are centred on the region of interest, such as the macula or optic nerve head | Peripapillary rings scans properly centred on the optic nerve; macular scans properly centred on the fovea | Crucial for accurate assessment as measurements can change substantially with poor centration |
| Segmentation quality | Assesses algorithm performance in layer segmentation | Segmentation lines should properly delineate the measurement areas; manual correction might be possible on certain devices if automated segmentation fails | Ensures reliable and reproducible layer thickness values |
| Light exposure control | Uniform exposure to prevent image saturation or darkness | Uniform illumination across image, which is optimised if the scan beam is placed centrally during the scanning process | Improves contrast and visibility for subtle details |
| Scan protocol adherence | Ensures consistency with predefined imaging protocols (eg, scan patterns, resolution, and field position) | Standardised scan protocols (eg, macular cube or peripapillary retinal nerve fibre layer scans); typically set by the study or clinical guidelines; consistent environment (eg, lights on or off in the scanning room) | Essential for ensuring imaging consistency and reliability, facilitating accurate comparisons across visits, sites, or studies |
| Registration to previous images | Aligns follow-up scans with previous images to ensure accurate comparison | Available on certain OCT devices with image registration capabilities | Might improve precision in longitudinal analysis and monitoring of disease progression |
| Retinal pathology | Identifies and documents any retinal abnormalities present in scans | Every scan, including each slice of volumetric scans, should be reviewed to inspect for pathology; scans must be evaluated by appropriately trained health-care providers | Ensures that significant findings are accurately identified and that timely referrals are made for further clinical evaluation and management |

OCT=optical coherence tomography.

***Table 2:*** **Summary of quality control considerations for OCT**

identification of optic nerve involvement. Tewarie and colleagues developed quality control guidelines for OCT in multiple sclerosis—known as the OSCAR-IB criteria.[92] The guidelines are now used both for OCT optic nerve scans, from which pRNFL thickness is derived, and macular scans, from which GCIPL thickness is derived. These guidelines were developed for use in people with multiple sclerosis participating in clinical trials, and to be used by trained readers. Therefore, whether the OSCAR-IB criteria could be applied in clinical practice is not yet determined. Nevertheless, we recommend using the OSCAR-IB criteria for the quality control of clinically acquired OCT scans to lower the risk of erroneous optic nerve involvement (table 2).

Several factors, including the stimulus parameters used, method of recording, and approaches for waveform analysis, influence VEPs, not only the recorded latencies, but also the sensitivity to optic nerve lesions. Additionally, the reliability and reproducibility of recordings can be influenced by electrical noise, the choice and placement of electrodes, impedance, and the number of averages obtained per recording session, among other factors.[94,95] We recommend following well established guidelines to ensure the use of appropriate parameters for doing VEPs in the clinic, such as the widely used standards from the International Society for Clinical Electrophysiology of Vision and the International Federation of Clinical Neurophysiology, which have probably contributed to improving VEP reliability and comparability across clinical laboratories.[46,94] Furthermore, diagnostic VEPs should be done and interpreted by certified, qualified, and experienced personnel and each centre should have its own normative dataset to define P100 latency delay or interocular asymmetry in VEP latencies that would classify the result as normal or abnormal.

Evaluation by an ophthalmologist, including a retinal specialist, might be necessary to aid the interpretation of unclear VEP and OCT abnormalities.

## Conclusions and future directions

In the 2024 revisions of the McDonald criteria for the diagnosis of multiple sclerosis, there are five anatomical

locations in which to assess dissemination in space—the periventricular, juxtacortical or cortical, infratentorial, spinal cord, and optic nerve locations.[25] Dissemination in space criteria are met with involvement of two or more of these five locations. There is ample evidence supporting the use of either OCT-derived pRNFL and GCIPL inter-eye differences, VEP-derived P100 latency delays, or optic nerve MRI[26] to identify optic nerve involvement. The exact degree of both absolute and relative VEP P100 latency delay is centre, technique, and device dependent, and normative data should be established for each clinical laboratory. Ensuring quality control is crucial when using OCT and VEPs to document optic nerve involvement, and the potential confounding effect of comorbidities on visual system measures, which merits further investigation, must be considered. Concurrent ophthalmological and neurological disorders that might produce similar OCT and VEP findings to those seen in multiple sclerosis might preclude the use of these tools in certain cases.

The possibility of bilateral optic nerve involvement in people with multiple sclerosis might be a limitation of relying on OCT inter-eye differences alone for the determination of optic nerve involvement. However, there is currently insufficient evidence regarding individual eye-derived measures of pRNFL or GCIPL thicknesses to establish consensus recommendations. Furthermore, Z-scores might have superior clinical use over raw retinal thickness measures, but warrant further investigation.[96] There might also be additive diagnostic value from using both pRNFL and GCIPL inter-eye differences. Additionally, further work is needed to assess whether VEPs and OCT in combination improve multiple sclerosis diagnostic performance over either technique alone, together with measures of visual function, such as low-contrast letter acuity.

There is also insufficient evidence that change in either OCT or VEP measures over time increases the specificity of multiple sclerosis diagnosis by satisfying traditional dissemination in time criteria. Moreover, neither VEPs nor OCT have been studied or validated to the same extent for their diagnostic use in paediatric multiple sclerosis compared with adult multiple sclerosis. Although the study of these tools in paediatric multiple sclerosis is a high-priority area of research, we currently do not recommend basing the determination of optic nerve involvement in children solely on either of these paraclinical tests.

Although the inclusion of optic nerve involvement has been shown to improve the diagnostic performance of the 2017 McDonald diagnostic criteria in Hispanic people with suspected multiple sclerosis, the effect of race and ethnicity on the detection of optic nerve involvement for multiple sclerosis diagnosis remains understudied and should be a subject of future research.[97]

Over time, we expect our recommendations to benefit from refinements and updates as further data emerge related to the use of combinations of OCT inter-eye differences, absolute thickness values from individual eyes, and combined and integrated use of both OCT and VEPs.

### Search strategy and selection criteria

References for this Personal View were identified by searches of PubMed from April 1, 2017, to Dec 31, 2024, and references from relevant articles. The search terms "multiple sclerosis", "MS", "optical coherence tomography", "OCT", "visual evoked potential", "VEP", "magnetic resonance imaging", "MRI", "optic neuropathy", "optic neuritis", "pediatric onset MS", "primary progressive MS", and "PPMS" were used. The final reference list was generated on the basis of relevance to the topics covered in this Personal View.

**Contributors**

SS, AJG, AT, XM, TC, and PAC delivered the topic presentation. SS, LL, AV-J, and PAC prepared the initial draft of the manuscript. All authors participated in discussion and reaching consensus, reviewed the manuscript draft, and approved the final manuscript for publication.

**Declaration of interests**

SS has received consulting fees from Medical Logix for the development of continuing medical education programmes in neurology; has served on scientific advisory boards for Amgen, Biogen, Clene, ImmPACT Bio, Genentech, Horizon Therapeutics, Novartis Pharmaceuticals, and ReWind Therapeutics; has been a consultant for Biogen, Genentech, InnoCare Pharma, Kiniksa, LAPIX Therapeutics, Novartis Pharmaceuticals, June Brain, and Setpoint Medical; is the Principal Investigator of investigator-initiated studies funded by Biogen, Genentech, and Novartis Pharmaceutics; has received support from the Race to Erase Multiple Sclerosis Foundation; was the site investigator of trials sponsored by Clene and MedDay; and is the Site Investigator of trials sponsored by LAPIX Therapeutics and Novartis Pharmaceuticals. AJG reports grants from the National Institute of Neurological Disorder and Stroke, National Multiple Sclerosis Society (NMSS), All May See, Westridge Foundation, Hoffman-La Roche; has received financial compensation for activities as an expert witness; is an Associate Editor at *JAMA Neurology*; and has participated in consulting for Pipeline Pharmaceuticals and Cognito Therapeutics. AV-J has received research support from Fondo de Investigación en Salud (PI17/02162 and PI22/01589) from Instituto de Salud Carlos III, Spain, and in the past 24 months has engaged in consulting for Roche, Novartis, Lundbeck, Merck, and Sanofi. XM's institution has received compensation for lecture honoraria from Peervoice, Excemed, Medscape; travel expenses from the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) and NMSS; fees for advisory board participation from Bial PD, Bristol-Myers Squibb/Celgene, Genzyme, Hoffmann-La Roche, Janssen Pharmaceuticals, Merck, Neuraxpharm, Novartis, and Samsung-Biosys; compensation for clinical trial steering committee membership from Bristol-Myers Squibb/Celgene, Hoffmann-La Roche, Novartis, and Sanofi-Genzyme. GB has received travel funding from Biogen, Merck, Novartis, Roche, Sanofi, and Teva; has received speaker honoraria from Biogen, Celgene/Bristol-Myers Squibb, Heidelberg Engineering, Janssen, Lilly, Medwhizz, Merck, Neuraxpharm, Novartis, Roche, Sanofi, Teva, and Zeiss; has received honoraria for consulting from Biogen, Celgene/Bristol-Myers Squibb, Janssen, Merck, Novartis, Roche, Sanofi-Genzyme, Adivo Associates, and Teva; has received unrestricted research grants from Celgene/Bristol-Myers Squibb, and Novartis; and serves on the executive committee of ECTRIMS. OO has received consulting fees from Roche, Novartis, Merck, and Amgen; has received travel and congress funding from Novartis, Biogen, Roche, Alexion, and Amgen; and has received grant support from Roche. AP has received grant support for remyelination trials in multiple sclerosis, paid to the Multiple Sclerosis Centre, Department of Neurology,

Amsterdam University Medical Centre (RESTORE trial); has received royalties or licenses from Up-to-Date (Wolters Kluver); and is a board member of the National Dutch Neuro-ophthalmology Association. FP has received honoraria from Alexion, Bayer, Biogen, Chugai, MerckSerono, Novartis, Genyzme, Amgen/Horizon/MedImmune, Roche, Sandoz, Shire, and Teva; research support from Alexion, Roche, Merck, Novartis, and Medimmune/Horizon/Amgen; serves on scientific advisory boards for Alexion, MedImmune, and Novartis; has received funding from Deutsche Forschungsgemeinschaft (DFG Exc 257), Bundesministerium für Bildung und Forschung (Competence Network Multiple Sclerosis), Guthy Jackson Charitable Foundation, EU Framework Program 7, and the National Multiple Sclerosis Society of the USA; and serves on the Editorial Board of *Neurology, Neuroimmunology & Neuroinflammation*. LJB receives funding by contract from the National Institutes of Health Common Fund and National Eye Institute Oculomics Initiative. PAC has received consulting fees and remuneration for serving on a scientific advisory board from Eli Lilly, Biogen, and Novartis; and is Principal Investigator on grants to Johns Hopkins University from Genentech and Setpoint Medical. All other authors declare no competing interests.

**Acknowledgments**

We thank Nik Krajnc for his assistance in designing figure 1, and Ting-Yi Lin for his assistance in developing supplementary tables 2–4.

**References**

1 Balcer LJ. Clinical practice. Optic neuritis. *N Engl J Med* 2006; **354:** 1273–80.
2 Ikuta F, Zimmerman HM. Distribution of plaques in seventy autopsy cases of multiple sclerosis in the United States. *Neurology* 1976; **26:** 26–28.
3 Toussaint D, Perier O, Verstappen A, Bervoets S. Clinicopathological study of the visual pathways, eyes, and cerebral hemispheres in 32 cases of disseminated sclerosis. *J Clin Neuroophthalmol* 1983; **3:** 211–20.
4 McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol* 2001; **50:** 121–27.
5 Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018; **17:** 162–73.
6 Kanamori A, Catrinescu MM, Belisle JM, Costantino S, Levin LA. Retrograde and Wallerian axonal degeneration occur synchronously after retinal ganglion cell axotomy. *Am J Pathol* 2012; **181:** 62–73.
7 Kerrison JB, Flynn T, Green WR. Retinal pathologic changes in multiple sclerosis. *Retina* 1994; **14:** 445–51.
8 Goldby F. A note on transneuronal atrophy in the human lateral geniculate body. *J Neurol Neurosurg Psychiatry* 1957; **20:** 202–07.
9 Wright PW, Archambault AS, Peek S, et al. Functional connectivity alterations in a murine model of optic neuritis. *Exp Neurol* 2017; **295:** 18–22.
10 Jindahra P, Petrie A, Plant GT. The time course of retrograde trans-synaptic degeneration following occipital lobe damage in humans. *Brain* 2012; **135:** 534–41.
11 Donaldson L, Chen M, Margolin E. Transsynaptic ganglion cell degeneration in adult patients after occipital lobe stroke. *J Neuroophthalmol* 2022; **43:** 243–47.
12 Murphy OC, Sotirchos ES, Kalaitzidis G, et al. Trans synaptic degeneration following acute optic neuritis in multiple sclerosis. *Annals Neurol* 2023; **93:** 76–87.
13 Petzold A, de Boer JF, Schippling S, et al. Optical coherence tomography in multiple sclerosis: a systematic review and meta-analysis. *Lancet Neurol* 2010; **9:** 921–32.
14 Dutta R, Trapp BD. Mechanisms of neuronal dysfunction and degeneration in multiple sclerosis. *Prog Neurobiol* 2011; **93:** 1–12.
15 Mahad DH, Trapp BD, Lassmann H. Pathological mechanisms in progressive multiple sclerosis. *Lancet Neurol* 2015; **14:** 183–93.
16 Salapa HE, Lee S, Shin Y, Levin MC. Contribution of the degeneration of the neuro-axonal unit to the pathogenesis of multiple sclerosis. *Brain Sci* 2017; **7:** 69.
17 Franklin RJM, Ffrench-Constant C. Remyelination in the CNS: from biology to therapy. *Nat Rev Neurosci* 2008; **9:** 839–55.
18 Franklin RJM, Simons M. CNS remyelination and inflammation: From basic mechanisms to therapeutic opportunities. *Neuron* 2022; **110:** 3549–65.
19 Cusato K, Stagg SB, Reese BE. Two phases of increased cell death in the inner retina following early elimination of the ganglion cell population. *J Comp Neurol* 2001; **439:** 440–49.
20 Kim KH, Puoris'haag M, Maguluri GN, et al. Monitoring mouse retinal degeneration with high-resolution spectral-domain optical coherence tomography. *J Vis* 2008; **8:** 17·1–11.
21 Peinado-Ramón P, Salvador M, Villegas-Pérez MP, Vidal-Sanz M. Effects of axotomy and intraocular administration of NT-4, NT-3, and brain-derived neurotrophic factor on the survival of adult rat retinal ganglion cells. A quantitative in vivo study. *Invest Ophthalmol Vis Sci* 1996; **37:** 489–500.
22 Villegas Pérez M, Vidal Sanz M, Rasminsky M, Bray GM, Aguayo AJ. Rapid and protracted phases of retinal ganglion cell loss follow axotomy in the optic nerve of adult rats. *J Neurobiol* 1993; **24:** 23–36.
23 Nadal-Nicolas FM, Jimenez-Lopez M, Sobrado-Calvo P, et al. Brn3a as a marker of retinal ganglion cells: qualitative and quantitative time course studies in naive and optic nerve-injured retinas. *Invest Ophthalmol Vis Sci* 2009; **50:** 3860–68.
24 Green AJ, McQuaid S, Hauser SL, Allen IV, Lyness R. Ocular pathology in multiple sclerosis: retinal atrophy and inflammation irrespective of disease duration. *Brain* 2010; **133:** 1591–601.
25 Montalban X, Lebrun-Frénay C, Oh J, et al. Diagnosis of multiple sclerosis: 2024 revisions of the McDonald criteria. *Lancet Neurol* 2025; **24:** 850–65.
26 Barkhof F, Reich DS, Oh J, et al. 2024 MAGNIMS–CMSC–NAIMS consensus recommendations on the use of MRI for the diagnosis of multiple sclerosis. *Lancet Neurol* 2025; **24:** 866–79.
27 Hrynchak P, Simpson T. Optical coherence tomography: an introduction to the technique and its use. *Optom Vis Sci* 2000; **77:** 347–56.
28 Frohman EM, Fujimoto JG, Frohman TC, Calabresi PA, Cutter G, Balcer LJ. Optical coherence tomography: a window into the mechanisms of multiple sclerosis. *Nat Clin Pract Neurol* 2008; **4:** 664–75.
29 Nguyen J, Rothman A, Fitzgerald K, et al. Visual pathway measures are associated with neuropsychological function in multiple sclerosis. *Curr Eye Res* 2018; **43:** 941–48.
30 Saidha S, Al-Louzi O, Ratchford JN, et al. Optical coherence tomography reflects brain atrophy in multiple sclerosis: a four-year study. *Ann Neurol* 2015; **78:** 801–13.
31 Saidha S, Sotirchos ES, Oh J, et al. Relationships between retinal axonal and neuronal measures and global central nervous system pathology in multiple sclerosis. *JAMA Neurol* 2013; **70:** 34–43.
32 Saidha S, Syc SB, Durbin MK, et al. Visual dysfunction in multiple sclerosis correlates better with optical coherence tomography derived estimates of macular ganglion cell layer thickness than peripapillary retinal nerve fiber layer thickness. *Mult Scler* 2011; **17:** 1449–63.
33 Ratchford JN, Saidha S, Sotirchos ES, et al. Active MS is associated with accelerated retinal ganglion cell/inner plexiform layer thinning. *Neurology* 2013; **80:** 47–54.
34 Syc SB, Warner CV, Hiremath GS, et al. Reproducibility of high-resolution optical coherence tomography in multiple sclerosis. *Mult Scler* 2010; **16:** 829–39.
35 Saidha S, Syc SB, Ibrahim MA, et al. Primary retinal pathology in multiple sclerosis as detected by optical coherence tomography. *Brain* 2011; **134:** 518–33.
36 Mwanza J, Oakley JD, Budenz DL, Chang RT, Knight OJ, Feuer WJ. Macular ganglion cell-inner plexiform layer: automated detection and thickness reproducibility with spectral domain-optical coherence tomography in glaucoma. *Invest Ophthalmol Vis Sci* 2011; **52:** 8323–29.
37 Paul F, Calabresi PA, Barkhof F, et al. Optical coherence tomography in multiple sclerosis: a 3-year prospective multicenter study. *Ann Clin Transl Neurol* 2021; **8:** 2235–51.
38 Petzold A, Fraser CL, Abegg M, et al. Diagnosis and classification of optic neuritis. *Lancet Neurol* 2022; **21:** 1120–34.

39 Petzold A, Liu Y, The International Consortium on Optic Neuritis. Application of diagnostic criteria for optic neuritis—authors' reply. *Lancet Neurol* 2023; **22:** 376–77.

40 Duvigneaud Z, Lardeux P, Verrecchia S, Benyahya L, Marignier R, Froment Tilikete C. Diagnostic criteria for optic neuritis in the acute and subacute phase: clinical uses and limitations. *J Neurol* 2024; **271:** 5629–36.

41 Klyscz P, Asseyer S, Alonso R, et al. Application of the international criteria for optic neuritis in the Acute Optic Neuritis Network. *Ann Clin Transl Neurol* 2024; **11:** 2473–84.

42 Leocani L, Guerrieri S, Comi G. Visual evoked potentials as a biomarker in multiple sclerosis and associated optic neuritis. *J Neuroophthalmol* 2018; **38:** 350–57.

43 Kothari R, Bokariya P, Singh S, Singh R. A comprehensive review on methodologies employed for visual evoked potentials. *Scientifica* 2016; **2016:** 9852194.

44 Cordano C, Sin JH, Timmons G, et al. Validating visual evoked potentials as a preclinical, quantitative biomarker for remyelination efficacy. *Brain* 2022; **145:** 3943–52.

45 Sarnthein J, Andersson M, Zimmermann MB, Zumsteg D. High test-retest reliability of checkerboard reversal visual evoked potentials (VEP) over 8 months. *Clin Neurophysiol* 2009; **120:** 1835–40.

46 Odom JV, Bach M, Brigell M, et al. ISCEV standard for clinical visual evoked potentials: (2016 update). *Doc Ophthalmol* 2016; **133:** 1–9.

47 Castoldi V, Marenna S, d'Isa R, et al. Non-invasive visual evoked potentials to assess optic nerve involvement in the dark agouti rat model of experimental autoimmune encephalomyelitis induced by myelin oligodendrocyte glycoprotein. *Brain Pathol* 2020; **30:** 137–50.

48 Marenna S, Huang S, Dalla Costa G, et al. Visual evoked potentials to monitor myelin cuprizone-induced functional changes. *Front Neurosci* 2022; **16:** 820155.

49 Davies MB, Williams R, Haq N, Pelosi L, Hawkins CP. MRI of optic nerve and postchiasmal visual pathways and visual evoked potentials in secondary progressive multiple sclerosis. *Neuroradiology* 1998; **40:** 765–70.

50 Petzold A, Balcer LJ, Calabresi PA, et al. Retinal layer segmentation in multiple sclerosis: a systematic review and meta-analysis. *Lancet Neurol* 2017; **16:** 797–812.

51 Balcer L, Balk L, Brandt A, et al. The International Multiple Sclerosis Visual System Consortium : advancing visual system research in multiple sclerosis. *J Neuroophthalmol* 2018; **38:** 494–501.

52 Nolan-Kenney RC, Liu M, Akhand O, et al. Optimal intereye difference thresholds by optical coherence tomography in multiple sclerosis: an international study. *Ann Neurol* 2019; **85:** 618–29.

53 Bsteh G, Hegen H, Altmann P, et al. Validation of inter-eye difference thresholds in optical coherence tomography for identification of optic neuritis in multiple sclerosis. *Mult Scler Relat Disord* 2020; **45:** 102403.

54 Cadavid D, Balcer L, Galetta S, et al. Safety and efficacy of opicinumab in acute optic neuritis (RENEW): a randomised, placebo-controlled, phase 2 trial. *Lancet Neurol* 2017; **16:** 189–99.

55 Jones SJ. Visual evoked potentials after optic neuritis. Effect of time interval, age and disease dissemination. *J Neurol* 1993; **240:** 489–94.

56 Frederiksen JL, Petrera J. Serial visual evoked potentials in 90 untreated patients with acute optic neuritis. *Surv Ophthalmol* 1999; **44** (suppl 1): 54.

57 Brusa A, Jones SJ, Plant GT. Long-term remyelination after optic neuritis: a 2-year visual evoked potential and psychophysical serial study. *Brain* 2001; **124:** 468–79.

58 Paty DW, Oger JJ, Kastrukoff LF, et al. MRI in the diagnosis of MS: a prospective study with comparison of clinical evaluation, evoked potentials, oligoclonal banding, and CT. *Neurology* 1988; **38:** 180–85.

59 Filippini G, Comi GC, Cosi V, et al. Sensitivities and predictive values of paraclinical tests for diagnosing multiple sclerosis. *J Neurol* 1994; **241:** 132–37.

60 Lee KH, Hashimoto SA, Hooge JP, et al. Magnetic resonance imaging of the head in the diagnosis of multiple sclerosis: a prospective 2-year follow-up with comparison of clinical evaluation, evoked potentials, oligoclonal banding, and CT. *Neurology* 1991; **41:** 657–60.

61 Gabelic T, Radmilovic M, Posavec V, et al. Differences in oligoclonal bands and visual evoked potentials in patients with radiologically and clinically isolated syndrome. *Acta Neurol Belg* 2013; **113:** 13–17.

62 Martinelli V, Dalla Costa G, Messina MJ, et al. Multiple biomarkers improve the prediction of multiple sclerosis in clinically isolated syndromes. *Acta Neurol Scand* 2017; **136:** 454–61.

63 Vidal-Jordana A, Rovira A, Arrambide G, et al. Optic Nerve topography in multiple sclerosis diagnosis: the utility of visual evoked potentials. *Neurology* 2021; **96:** e482–90.

64 Vidal-Jordana A, Rovira A, Calderon W, et al. Adding the optic nerve in multiple sclerosis diagnostic criteria: a longitudinal, prospective, multicenter study. *Neurology* 2024; **102:** e200805.

65 Davion J, Lopes R, Drumez E, et al. Asymptomatic optic nerve lesions: an underestimated cause of silent retinal atrophy in MS. *Neurology* 2020; **94:** e2468–78.

66 Outteryck O, Lopes R, Drumez E, et al. Optical coherence tomography for detection of asymptomatic optic nerve lesions in clinically isolated syndrome. *Neurology* 2020; **95:** e733–44.

67 Tajfirouz D, Madhavan A, Pacheco Marrero JM, et al. Frequency of asymptomatic optic nerve enhancement in 203 patients with MOG antibody-associated disease. *Neurol Neuroimmunol Neuroinflamm* 2024; **11:** e200277.

68 Shah SS, Morris P, Buciuc M, et al. Frequency of asymptomatic optic nerve enhancement in a large retrospective cohort of patients with aquaporin-4+ NMOSD. *Neurology* 2022; **99:** e851–57.

69 Polman CH, Koetsier JC, Wolters EC. Multiple sclerosis: incorporation of results of laboratory techniques in the diagnosis. *Clin Neurol Neurosurg* 1985; **87:** 187–92.

70 Beer S, Rosler KM, Hess CW. Diagnostic value of paraclinical tests in multiple sclerosis: relative sensitivities and specificities for reclassification according to the Poser committee criteria. *J Neurol Neurosurg Psychiatry* 1995; **59:** 152–59.

71 Matthews WB, Wattam-Bell JR, Pountney E. Evoked potentials in the diagnosis of multiple sclerosis: a follow up study. *J Neurol Neurosurg Psychiatry* 1982; **45:** 303–07.

72 Hume AL, Waxman SG. Evoked potentials in suspected multiple sclerosis: diagnostic value and prediction of clinical course. *J Neurol Sci* 1988; **83:** 191–210.

73 Leocani L, Rovaris M, Boneschi FM, et al. Multimodal evoked potentials to assess the evolution of multiple sclerosis: a longitudinal study. *J Neurol Neurosurg Psychiatry* 2006; **77:** 1030–35.

74 Stevenson VL, Miller DH, Rovaris M, et al. Primary and transitional progressive MS: a clinical and MRI cross-sectional study. *Neurology* 1999; **52:** 839–45.

75 Bsteh G, Hegen H, Altmann P, et al. Diagnostic performance of adding the optic nerve region assessed by optical coherence tomography to the diagnostic criteria for multiple sclerosis. *Neurology* 2023; **101:** e784–93.

76 Bennett JL, Costello F, Chen JJ, et al. Optic neuritis and autoimmune optic neuropathies: advances in diagnosis and treatment. *Lancet Neurol* 2023; **22:** 89–100.

77 Behbehani R. Clinical approach to optic neuropathies. *Clin Ophthalmol* 2007; **1:** 233–46.

78 Salehi MA, Nowroozi A, Gouravani M, Mohammadi S, Arevalo JF. Associations of refractive errors and retinal changes measured by optical coherence tomography: a systematic review and meta-analysis. *Surv Ophthalmol* 2022; **67:** 591–607.

79 Wang X, Chen Y, Wang Z, et al. Assessment of macular structures and vascular characteristics in highly myopic anisometropia using swept-source optical coherence tomography angiography. *Front Physiol* 2022; **13:** 918393.

80 MacIntosh PW, Kumar SV, Saravanan VR, Shah VM. Acute changes in ganglion cell layer thickness in ischemic optic neuropathy compared to optic neuritis using optical coherence tomography. *Int J Ophthalmol* 2020; **13:** 120–23.

81 Erlich-Malona N, Mendoza-Santiesteban CE, Hedges TR 3rd, Patel N, Monaco C, Cole E. Distinguishing ischaemic optic neuropathy from optic neuritis by ganglion cell analysis. *Acta Ophthalmol* 2016; **94:** e721–26.

82 Murphy O, Calabresi P, Saidha S. Trans-synaptic degeneration as a mechanism of neurodegeneration in multiple sclerosis. *Neural Regen Res* 2023; **18:** 2682–84.

83 Al-Louzi O, Button J, Newsome SD, Calabresi PA, Saidha S. Retrograde trans-synaptic visual pathway degeneration in multiple sclerosis: a case series. *Mult Scler* 2017; **23:** 1035–39.

84 Roca-Fernandez A, Camera V, Loncarevic-Whitaker G, et al. The use of OCT in good visual acuity MOGAD and AQP4-NMOSD patients; with and without optic neuritis. *Mult Scler J Exp Transl Clin* 2021; **7:** 20552173211066446.

85 Oertel FC, Zimmermann HG, Motamedi S, et al. Retinal changes in double-antibody seronegative neuromyelitis optica spectrum disorders. *Neurol Neuroimmunol Neuroinflamm* 2024; **11:** e200273.

86 Lin T, Chien C, Lu A, Paul F, Zimmermann HG. Retinal optical coherence tomography and magnetic resonance imaging in neuromyelitis optica spectrum disorders and MOG-antibody associated disorders: an updated review. *Expert Rev Neurother* 2021; **21:** 1101–23.

87 Sotirchos ES, Filippatou A, Fitzgerald KC, et al. Aquaporin-4 IgG seropositivity is associated with worse visual outcomes after optic neuritis than MOG-IgG seropositivity and multiple sclerosis, independent of macular ganglion cell layer thinning. *Mult Scler* 2020; **26:** 1360–71.

88 Chen JJ, Sotirchos ES, Henderson AD, et al. OCT retinal nerve fiber layer thickness differentiates acute optic neuritis from MOG antibody-associated disease and Multiple Sclerosis: RNFL thickening in acute optic neuritis from MOGAD *vs* MS. *Mult Scler Relat Disord* 2022; **58:** 103525.

89 Petzold A, Chua SYL, Khawaja AP, et al. Retinal asymmetry in multiple sclerosis. *Brain* 2021; **144:** 224–35.

90 Cruz-Herranz A, Balk LJ, Oberwahrenbrock T, et al. The APOSTEL recommendations for reporting quantitative optical coherence tomography studies. *Neurology* 2016; **86:** 2303–09.

91 Aytulun A, Cruz-Herranz A, Aktas O, et al. APOSTEL 2·0 recommendations for reporting quantitative optical coherence tomography studies. *Neurology* 2021; **97:** 68–79.

92 Tewarie P, Balk L, Costello F, et al. The OSCAR-IB consensus criteria for retinal OCT quality assessment. *PLoS One* 2012; **7:** e34823.

93 Schippling S, Balk LJ, Costello F, et al. Quality control for retinal OCT in multiple sclerosis: validation of the OSCAR-IB criteria. *Mult Scler* 2015; **21:** 163–70.

94 Holder GE, Celesia GG, Miyake Y, Tobimatsu S, Weleber RG, International Federation of Clinical Neurophysiology. International Federation of Clinical Neurophysiology: recommendations for visual system testing. *Clin Neurophysiol* 2010; **121:** 1393–409.

95 Janaky M, Janossy A, Horvath G, Benedek G, Braunitzer G. VEP and PERG in patients with multiple sclerosis, with and without a history of optic neuritis. *Doc Ophthalmol* 2017; **134:** 185–93.

96 Lin T, Motamedi S, Asseyer S, et al. Individual prognostication of disease activity and disability worsening in multiple sclerosis with retinal layer thickness Z scores. *Neurol Neuroimmunol Neuroinflamm* 2024; **11:** e200269.

97 Amezcua L, Robers MV, Soneji D, Manouvakhova O, Martinez A, Islam T. Inclusion of optic neuritis in dissemination in space improves the performance of McDonald 2017 criteria in Hispanic people with suspected multiple sclerosis. *Mult Scler* 2023; **29:** 1748–54.