Section Editor: Fiona Costello, MD, FRCP(C)

From the Section Editor: The next two installments in the JNO "Disease of the Year: Multiple Sclerosis" series focus on lessons that can be learned form the afferent visual pathway, as a putative model of MS. In their article entitled, "Visual evoked potentials as a biomarker in multiple sclerosis and associated optic neuritis" Leocani and colleagues highlight the role of visual evoked potential (VEP) testing as a means of capturing the effects of demyelination, remyelination, and associated neuroaxonal injury in the central nervous system (CNS). Conjointly, Horton and Bennett discuss the acute management of optic neuritis, which is aptly described as an "evolving paradigm." In their state-of-the art overview of the topic, these authors explore the spectrum of inflammatory optic neuropathies, with emphasis on clinical features, neuroimaging findings, and serological markers that help refine diagnosis, and target appropriate treatment strategies. When considered holistically, these reviews prompt us to consider how VEP and other surrogate endpoints can be used to differentiate subtypes of optic neuritis that may ultimately herald a wide variety of CNS inflammatory disorders.

Visual Evoked Potentials as a Biomarker in Multiple Sclerosis and Associated Optic Neuritis

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Abstract: Multiple sclerosis (MS) is an inflammatory, degenerative disease of the central nervous system (CNS) characterized by progressive neurological decline over time. The need for better "biomarkers" to more precisely capture and track the effects of demyelination, remyelination, and associated neuroaxonal injury is a well-recognized challenge in the field of MS. To this end, visual evoked potentials (VEPs) have a role in assessing the extent of demyelination along the optic nerve, as a functionally eloquent CNS region. Moreover, VEPs testing can be used to predict the extent of recovery after optic neuritis (ON) and capture disabling effects of clinical and subclinical demyelination events in the afferent visual pathway. In this review, the evolving role of VEPs in the diagnosis of patients with ON and MS and the utility of VEPs testing in determining therapeutic benefits of emerging MS treatments is discussed.

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BACKGROUND

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) and the leading cause of neurologic disability in young adults. Acute optic neuritis (ON), reported as the onset manifestation in up to one-third of MS cases, may affect up to 70% of patients with MS during the course of their disease (1–3). In addition, involvement of the retrochiasmatic visual pathway may impair visual function.

Full-field visual evoked potentials (ff-VEPs) have been performed in clinical practice since the 1970s to assess conduction along the visual pathways with diagnostic, monitoring and prognostic purpose. Visual evoked potential guidelines were updated in 2010 by the International Federation of Clinical Neurophysiology (4) and in 2016 by the International Society for Clinical Electrophysiology of Vision (ISCEV) (5). In 1994, Baseler et al (6) described the technique of multifocal VEPs (mf-VEPs), which tested discrete portions of the visual field (7). Since then, in addition to glaucoma (8), mf-VEPs have been used to assess other optic neuropathies and neurological conditions including MS.

This review examines the current and potential future applications of VEPs as a biomarker in MS and associated ON.

EVIDENCE ACQUISITION

We searched PubMed database up to April 30, 2018, using the terms "visual evoked potentials AND multiple sclerosis," "visual evoked potentials AND optic neuritis." For clinical trials, the https://clinicaltrials.gov/webpage was searched.

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VISUAL EVOKED POTENTIALS IN THE DIAGNOSIS OF MULTIPLE SCLEROSIS AND OPTIC NEURITIS

VEPs are used to confirm the presence of visual pathology or to detect subclinical asymptomatic involvement of the visual pathway. The presence of increased latency with preserved waveform morphology has been considered a sign of a demyelinating process (9). Early studies showed a prevalence of increased VEP latency in up to 50%–70% of patients with MS without visual complaints (10–12). More recently, the sensitivity of VEP in patients without a history of ON has been reported to be 20%–50% (13,14). However, this sensitivity is, in part, dependent on the timing of the testing. VEPs have been reported as abnormal in 90% of patients tested within 6 months from onset of ON symptoms, but in about 70% when more than 2 years have elapsed (15). Naismith et al (16) reported a sensitivity of 81% for ff-VEPs in 96 eyes experiencing ON at least 6 months previously with similar findings reported by Di Maggio et al (17). Fredriksen and Petrera (18) reported ff-VEPs to be abnormal in 77% of acute ON eyes at onset and in 89% at one or more follow-up sessions, with progressive normalization in 19% over 1 year. The overall sensitivity in MS has been reported up to 85% (9), with differences according to disease duration and course, reaching 90% in progressive MS (19) and ranging from 25% to 50% in clinically isolated syndrome (CIS), regardless of the initial neurologic signs and symptoms (20–23).

Normal ff-VEPs cannot exclude the presence of a lesion involving only a portion of optic nerve fibers, or lesions with short longitudinal extension without a significant latency increase (9), or partial retrochiasmal lesions.

VEPs were included in the diagnostic criteria of primary progressive MS in the original McDonald criteria (24) and in the first revision (25), but not in subsequent revisions (26,27). The most recent McDonald criteria include VEPs as a means to detect of a demyelinating process in patients presenting with visual symptoms (26,27).

Multifocal VEPs were reported as more sensitive compared with standard ff-VEPs both in symptomatic and asymptomatic eyes of patients with MS (28,29) and with promising results in patients with CIS (30). In 26 individuals with unilateral ON, ff-VEPs abnormalities were found in 73% and mf-VEP in 89% and with superior performance in detecting small or peripheral visual field defects (28). In non-ON eyes of 29 patients with CIS, mf-VEP amplitude was abnormal in 48.3% and latency in 20.7% (30). These features have been confirmed in a cohort of 145 patients with MS with 65% abnormal responses in non-ON eyes and up to 90% in ON eyes (31). Similar results had been previously reported by Fraser et al (32) with a different testing equipment (Accumap; ObjectiVision, Sydney, Australia), with mf-VEPs abnormal in 97.3% of ON eyes (previous or acute), whereas Nebbioso et al (33) found ff-VEPs more sensitive than mf-VEPs (using the Vision Monitor MonPack 120 by Metrovision) in a cohort of 24 patients with acute ON (90.9% vs 77.2%, respectively). These discrepancies may be related to differences in equipment and techniques used as well as patient selection.

VEPs have been used to differentiate MS from other inflammatory CNS diseases such as neuromyelitis optica spectrum disorder (NMOSD). Two studies found that P100 latency was more delayed in MS than in NMOSD, with greater proportion of absent responses and less frequent subclinical alterations in the latter group (34,35). These data were obtained in patients of Afro-Brazilian and Japanese origin. By contrast, a study of white patients found more heterogeneous VEP abnormalities in NMOSD (36).

PROGNOSTIC ROLE OF VISUAL EVOKED POTENTIALS IN MULTIPLE SCLEROSIS AND OPTIC NEURITIS

The prognostic value of VEPs can be assessed in 3 ways: predicting the degree of optic nerve damage and, thus, the long-term visual outcome; predicting the risk of developing MS in patients with CIS; and predicting future disability in patients who already have a diagnosis of MS.

After an ON attack, the final visual outcome is not totally predictable by ff-VEPs recorded in the acute phase. Yet, the presence of preserved cortical responses, despite increased latency, is an indicator of partial demyelinating damage suggesting good visual recovery. However, the absence of cortical responses is not necessarily associated with a poor functional outcome, potentially indicating only transient conduction block (37). The persistence of morphological alterations of ff-VEPs beyond 4 months is predictive of a long-term visual impairment. The reappearance of initially absent waveforms, despite their delay in latency, has favorable prognostic implications (38). Although optic nerve lesions tend to remyelinate at a specific rate, smaller lesions seem to recovery more completely with respect to VEP waveform morphology (39). Brain plasticity also seems to play a major role in the recovery of vision after ON (40), possibly offsetting some of the effects of optic nerve damage and mitigating the functional consequences of optic nerve dysfunction.

Several studies over the past 30 years have explored the association between ff-VEPs and subsequent development of MS with variable conclusions. From some studies of the 1980s and early 1990s, a significant association between ff-VEPs alteration in patients with various initial neurological manifestations and MS development emerged, with risk increasing from 2.5- to 9-fold (41–43). A prospective multicenter study on 82 patients with suspected MS found only mild positive and negative predictive values (26% and 62%, respectively) in relation to ff-VEP results and development of MS over a mean follow-up of 2.9 years (20). However,

the inclusion of a not irrelevant proportion of patients with visual symptoms limited ff-VEP validation as biomarker of dissemination in space (20). A retrospective study of 243 patients with CIS diagnosed between 2000 and 2013 evaluated the prognostic role of multimodal evoked potentials with other multiple biomarkers, including magnetic resonance imaging (MRI) and cerebrospinal fluid data. The frequency of altered ff-VEPs did not differ between patients who did or did not develop MS (48.8% vs 49.1%, respectively) (22). Some investigators also analyzed if specific features of VEP responses in the early phase of ON had any prognostic value. Two studies using mf-VEPs found an increased risk of MS conversion in patients with significant increased latency associated with a reduction in amplitude (44,45), whereas another did not identify a relationship between ff-VEP after ON and development of MS (46). Patients with MRI findings placing them at higher risk for MS showed higher mean latency and lower mean amplitude values than low-risk patients (no demyelinating lesions on MRI) (47). This observation was supported by another study including 87 patients with ON, which demonstrated progressive deterioration over the first 12 months after ON episode of both amplitude and latency in fellow eyes to be highly suggestive of MS (48).

The cross-sectional and longitudinal correlation between VEPs and global and visual disability has been explored with conflicting evidence (19,37,45–51), because of differences in disease duration and variation in the definition of impairment, especially when assessing visual function. Mild visual pathway involvement may not alter visual acuity but affects other parameters of visual perception. A study on 21 patients with ON found a correlation between the persistence of conduction slowing (VEP latency) and motion perception abnormalities (52). Concerning global disability, it is important to point out the small impact of visual function has on the EDSS score. In a cohort of 28 patients with MS and mf-VEPs available, median EDSS was found to significantly differ between patients with normal or abnormal mf-VEPS amplitude values (53); in another report, a significant correlation was identified between the signal-to-noise ratio of mf-VEP amplitude and EDSS in 28 patients with clinically definite MS (54). Many of these studies also attempted to assess VEPs to predict disability, finding only moderate correlation between ff-VEPs and subsequent EDSS scores (19,49–51).

VISUAL EVOKED POTENTIALS TO MONITOR MULTIPLE SCLEROSIS AND OPTIC NEURITIS

Can evoked potentials, including VEPs, be used to monitor the natural history of MS and the potential effect of therapeutic interventions? The answer to this question should be cautiously interpreted because of the physiological variability over time of neurophysiological parameters: P100 waveform of ff-VEPs has a very good reproducibility in the general population, but there is a higher test–retest variability in patients with MS because of the complex interplay between demyelinating, remyelinating, and neurodegenerative processes (55,56). Therefore, the use of robust criteria to define the longitudinal changes of the visual response is crucial. Despite these concerns, there is evidence of overall reproducibility of VEPs in both single and multicenter studies (57,58). In this regard, mf-VEPs were reported as more reproducible than standard ff-VEPs (58), particularly considering waveform amplitude (59) with possible implications for their use as a correlate of neuroaxonal damage, as compared to latency, which is considered a measure of the demyelination extent.

Although several studies identified either no or equivocal correlations between the evolution over time of ff-VEPs and global or visual disability (19,55,60), other reports documented good correlations between neurophysiologic measures and clinical status (49,61–63). The explanation for these differing results may lie in the redundancy of the CNS, with neurophysiological alterations not necessarily accompanied by a concomitant clinical abnormality. However, these changes may represent a reduction of the functional reserve of a given pathway and have a negative prognostic connotation. In addition, there is a "ceiling effect" (disappearance of the waveform), particularly evident for ff-VEPs and limiting their usefulness in monitoring patients with advanced disease (19).

VEPs have been used as primary or secondary outcome measures in clinical trials, testing the effect of putative remyelinating and neuroprotective agents. The visual pathway has been proposed as a reliable model to uncover the mechanisms of CNS damage (64–66). Full field-VEPs were a secondary outcome measure in a double-blind, randomized, placebo-controlled trial testing the effect of IVIg in 68 patients with acute ON: no effect on ff-VEP latency was found. However, only average latency values were used between in the 2 groups (67). Full field-VEPs were used to test the effect of simvastatin given within 4 weeks from ON onset, with significant advantage of active treatment vs placebo on mean latency and amplitude values; however some differences in terms of VEPs response could be already outlined at baseline (68). The RENEW trial, as well as other previous phase 2 studies on erythropoietin and autologous mesenchymal stem cells, emphasized the importance of interindividual variability and variation over time of ff-VEP response, when gauging the therapeutic effect of a medication (69–71). The ReBUILD study documented a potential remyelinating role of clemastine fumarate in MS patients with a reduction in ff-VEP latency as positive primary outcome (72). Phenytoin administered within 2 weeks from ON onset was associated with a significant reduction in retinal nerve fiber layer (RNFL) and macular volume loss over time, without significant effect on ff-VEP parameters (73). The authors of this study concluded that more

sensitive measures of visual conduction such as mf-VEPs should be used in future trials (73). This latter technique has been included in a substudy of the RENEW trial (74) demonstrating anti–LINGO-1 treatment to prevent mf-VEP amplitude loss in the fellow eyes of patients with unilateral ON.

VISUAL EVOKED POTENTIALS COMPARISON WITH OTHER MEASURES

In general, good correlations between ff-VEP and mf-VEP parameters in MS and ON have been reported (28,29). Considering other measures, early studies in the 1970s and 1980s pointed out a limited correlation between ff-VEPs (in particular latency) and final visual acuity after an ON episode. However, better correlations do exist with other visual function tests such as visual field examination, color vision, and perception latency (75,76). Similarly, an association between mf-VEPs latency and visual acuity has been described in the acute phase of ON (56) but in the absence of any with visual recovery (45). Other studies identified a correlation in patients with MS between mf-VEP parameters and low-contrast visual acuity (77) as well as with contrast sensitivity (77,78). The multifocal technique has been suggested as a possible measure of the visual field (79) with mf-VEPs showing a higher sensitivity than and automated perimetry (mainly Humphrey visual field) (53,77,80,81).

Several studies combined VEPs testing with retinal structural measures using optical coherence tomography (OCT), to explore the relationship between demyelination and neuroaxonal degeneration. Good correlations between VEPs amplitude and RNFL thickness have been found for both ff-VEPs (82,83) and mf-VEPs (84,85). The latter technique also showed a high topographic correspondence with RNFL sectorial analysis. Several investigators identified a correlation between RNFL and ganglion cell layer thickness and VEP latency, especially in non-ON eyes (83,86–89), suggesting chronic subclinical demyelination may lead to progressive axonal loss. The relationship between demyelination and subsequent axonal loss seems instead to be less certain after ON (90–92). Comparative studies have reported a higher sensitivity in detecting abnormalities with ff-VEPs over OCT in patients with ON (16), MS (17), and CIS (93).

VEPs have been correlated with MRI findings, of both the optic nerve and the brain. At the optic nerve level, good correlations have been found between diffusion tensor imaging (DTI) and amplitude for ff-VEPs (94) and mf-VEPs (95,96). Less certain is the relationship between magnetization transfer imaging and VEP latency (97–102), suggesting magnetization transfer imaging may be not entirely specific for myelin. A more robust correlation has been described between VEPs latency and T2-STIR optic nerve lesion length (103,104). In patients with MS, mf-VEPs latency was found to correlate with optic radiation lesion load and DTI measures in eyes without previous ON, indicating the presence of retrochiasmal and, in particular, retrogeniculate lesions (105). Finally, mf-VEPs amplitude, analyzed for separate contralateral visual hemifields after acute ON, correlates with optic radiation DTI measures, suggesting the possibility of anterograde trans-synaptic degeneration (106,107).

OTHER VISUAL EVOKED POTENTIAL TECHNIQUES

It has been speculated that pattern-reversal VEPs to colored checks may be more useful than traditional black and white checks in differentiating the optic neuropathy of ON from that of glaucoma (108). However, the comparison of VEPs obtained in 30 patients with MS with equiluminant chromatic (red-green and blue-yellow) and achromatic stimuli, although confirming the general vulnerability of color-opponent visual pathways in this pathology, showed no statistically significant difference in terms of sensitivity between the 2 techniques (109). Other testing techniques requiring validation include steady-state VEPs to periodic visual stimuli (110) and low-contrast patterned stimuli, with ff-VEPs and mf-VEPs (83,111,112).

Finally, VEPs response can be obtained through flash stimulation. Intersubject variability is higher compared with pattern-reversal stimulation, but the flash technique still finds a role in several patient populations including young children, noncompliant individuals, and those suspected of functional neurological disorders or malingering (5).

CONCLUSIONS AND FUTURE PERSPECTIVES

ff-VEPs represent an important technique in clinical practice, able to rapidly explore the entire visual pathway and to provide robust information. Full field-VEPs can corroborate an attack of ON, and despite limited prognostic implications especially in the acute phase, if repeated over time can document conduction recovery. Evolution of ff-VEP results may guide the clinician to correctly interpret visual relapses, discriminating between ON mimickers (e.g., Uhthoff phenomenon) and new inflammatory events. This has important therapeutic implications. Although neurophysiology has been excluded from the latest version of the McDonald criteria for the diagnosis of MS (27), ff-VEPs should be considered a supportive paraclinical test in the routine assessment of patients with suspected MS.

mf-VEPs are a promising technique able to topographically assess conduction along the visual pathway, identifying partial defects, which may not alter standard ff-VEPs, and potentially allow for detailed function-structural analysis. mf-VEPs are primarily confined to the field of research because acquisition is time-consuming compared with ff-

VEPs and further standardization is required, particularly in the interpretation of testing results. In addition, the use of different stimuli such as low-contrast stimuli (83,111,112) may increase VEPs diagnostic and prognostic power (54,113–115).

REFERENCES

1. **Sørensen TL**, Frederiksen JL, Brønnum-Hansen H, Petersen HC. Optic neuritis as onset manifestation of multiple sclerosis: a nationwide, long-term survey. Neurology. 1999;53:473–478.
2. **Costello F**. The afferent visual pathway: designing a structural-functional paradigm of multiple sclerosis. ISRN Neurol. 2013:134858.
3. **Tintore M**, Rovira À, Río J, Otero-Romero S, Arrambide G, Tur C, Comabella M, Nos C, Arévalo MJ, Negrotto L, Galán I, Vidal-Jordana A, Castilló J, Palavra F, Simon E, Mitjana R, Auger C, Sastre-Garriga J, Montalban X. Defining high, medium and low impact prognostic factors for developing multiple sclerosis. Brain. 2015;138:1863–1874.
4. **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;121:1393–1409.
5. **Odom JV**, Bach M, Brigell M, Holder GE, McCulloch DL, Mizota A, Tormene AP; International Society for Clinical Electrophysiology of Vision. ISCEV standard for clinical visual evoked potentials: (2016 update). Doc Ophthalmol. 2016;133:1–9.
6. **Baseler HA**, Sutter EE, Klein SA, Carney T. The topography of visual evoked response properties across the visual field. Electroencephalogr Clin Neurophysiol. 1994;90:65–81.
7. **Klistorner A**, Graham SL, Grigg JR, Billson FA. Multifocal topographic visual evoked potential: improving objective detection of local visual field defects. Invest Ophthalmol Vis Sci. 1998;39:937–950.
8. **Goldberg I**, Graham S, Klistorner A. Multifocal objective perimetry in the detection of glaucomatous field loss. Am J Ophthalmol. 2002;133:29–39.
9. **Comi G**, Leocani L, Medaglini S, Locatelli T, Martinelli V, Santuccio G, Rossi P. Measuring evoked responses in multiple sclerosis. Mult Scler. 1999;5:263–267.
10. **Asselman P**, Chadwick DW, Marsden DC. Visual evoked responses in the diagnosis and management of patients suspected of multiple sclerosis. Brain. 1975;98:261–282.
11. **Celesia GG**. Evoked potential techniques in the evaluation of visual function. J Clin Neurophysiol. 1984;1:55–76.
12. **Halliday AM**, McDonald WI, Mushin I. Visual evoked potentials in patients with demyelinating disease. In: Desmedt JE, ed. Visual Evoked Potentials in Man: New Developments. Oxford, United Kingdom: Claredondon Press, 1977:438–449.
13. **Sisto D**, Trojano M, Vetrugno M, Trabucco T, Iliceto G, Sborgia C. Subclinical visual involvement in multiple sclerosis: a study by MRI, VEPs, frequency-doubling perimetry, standard perimetry, and contrast sensitivity. Invest Ophthalmol Vis Sci. 2005;46:1264–1268.
14. **Voitenkov V**, Skripchenko N, Klimkin A. Visual pathways involvement in clinically isolated syndrome in children. Int J Ophtalmol. 2015;8:382–384.
15. **Jones SJ**. Visual evoked potentials after optic neuritis. Effect of time interval, age and disease dissemination. J Neurol. 1993;240:489–494.
16. **Naismith RT**, Tutlam NT, Xu J, Shepherd JB, Klawiter EC, Song SK, Cross AH. Optical coherence tomography is less sensitive than visual evoked potentials in optic neuritis. Neurology. 2009;73:46–52.
17. **Di Maggio G**, Santangelo R, Guerrieri S, Bianco M, Ferrari L, Medaglini S, Rodegher M, Colombo B, Moiola L, Chieffo R, Del Carro U, Martinelli V, Comi G, Leocani L. Optical coherence tomography and visual evoked potentials: which is more sensitive in multiple sclerosis? Mult Scler. 2014;20:1342–1347.
18. **Frederiksen JL**, Petrera J. Serial visual evoked potentials in 90 untreated patients with acute optic neuritis. Surv Ophthalmol. 1999;44:S54–S62.
19. **Leocani L**, Rovaris M, Boneschi FM, Medaglini S, Rossi P, Martinelli V, Amadio S, Comi G. Multimodal evoked potentials to assess the evolution of multiple sclerosis: a longitudinal study. J Neurol Neurosurg Psychiatry. 2006;77:1030–1035.
20. **Filippini G**, Comi G, Cosi V, Bevilacqua L, Ferrarini M, Martinelli V, Bergamaschi R, Filippi M, Citterio A, D'Incerti L. Sensitivities and predictive values of paraclinical tests for diagnosing multiple sclerosis. J Neurol. 1994;241:132–137.
21. **Pelayo R**, Montalban X, Minoves T, Moncho D, Rio J, Nos C, Tur C, Castillo J, Horga A, Comabella M, Perkal H, Rovira A, Tintoré M. Do multimodal evoked potentials add information to MRI in clinically isolated syndromes? Mult Scler. 2010;16:55–61.
22. **Martinelli V**, Dalla Costa G, Messina MJ, Di Maggio G, Sangalli F, Moiola L, Rodegher M, Colombo B, Furlan R, Leocani L, Falini A, Comi G. Multiple biomarkers improve the prediction of multiple sclerosis in clinically isolated syndromes. Acta Neurol Scand. 2017;136:454–461.
23. **Gabelić T**, Radmilović M, Posavec V, Skvorc A, Bošković M, Adamec I, Milivojević I, Barun B, Habek M. Differences in oligoclonal bands and visual evoked potentials in patients with radiologically and clinically isolated syndrome. Acta Neurol Belg. 2013;113:13–17.
24. **McDonald WI**, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, McFarland HF, Paty DW, Polman CH, Reingold SC, Sandberg-Wollheim M, Sibley W, Thompson A, van den Noort S, Weinshenker BY, Wolinsky JS. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol. 2001;50:121–127.
25. **Polman CH**, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, Lublin FD, Metz LM, McFarland HF, O'Connor PW, Sandberg-Wollheim M, Thompson AJ, Weinshenker BG, Wolinsky JS. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria." Ann Neurol. 2005;58:840–846.
26. **Polman CH**, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, Fujihara K, Havrdova E, Hutchinson M, Kappos L, Lublin FD, Montalban X, O'Connor P, Sandberg-Wollheim M, Thompson AJ, Waubant E, Weinshenker B, Wolinsky JS. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011;69:292–302.
27. **Thompson AJ**, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, Correale J, Fazekas F, Filippi M, Freedman MS, Fujihara K, Galetta SL, Hartung HP, Kappos L, Lublin FD, Marrie RA, Miller AE, Miller DH, Montalban X, Mowry EM, Sorensen PS, Tintoré M, Traboulsee AL, Trojano M, Uitdehaag BMJ, Vukusic S, Waubant E, Weinshenker BG, Reingold SC, Cohen JA. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17:162–173.
28. **Klistorner A**, Fraser C, Garrick R, Graham S, Arvind H. Correlation between full-field and multifocal VEPs in optic neuritis. Doc Ophthalmol. 2008;116:19–27.
29. **Grover LK**, Hood DC, Ghadiali Q, Grippo TM, Wenick AS, Greenstein VC, Behrens MM, Odel JG. A comparison of multifocal and conventional visual evoked potential techniques in patients with optic neuritis/multiple sclerosis. Doc Ophthalmol. 2008;117:121–128.
30. **Pérez-Rico C**, Ayuso-Peralta L, Rubio-Pérez L, Roldán-Díaz I, Arévalo-Serrano J, Jiménez-Jurado D, Blanco R. Evaluation of visual structural and functional factors that predict the development of multiple sclerosis in clinically isolated syndrome patients. Invest Ophthalmol Vis Sci. 2014;55:6127–6131.
31. **Laron M**, Cheng H, Zhang B, Schiffman JS, Tang RA, Frishman LJ. Assessing visual pathway function in multiple sclerosis

patients with multifocal visual evoked potentials. Multi Scler. 2009;15:1431–1441.
32. **Fraser CL**, Klistorner A, Graham SL, Garrick R, Billson FA, Grigg JR. Multifocal visual evoked potential analysis of inflammatory or demyelinating optic neuritis. Ophthalmology. 2006;113:323e1–323e2.
33. **Nebbioso M**, Steigerwalt RD, Pecori-Giraldi J, Vingolo EM. Multifocal and pattern reversal visual evoked potentials vs. automated perimetry frequency-doubling technology matrix in optic neuritis. Indian J Ophthalmol. 2013;61:59–64.
34. **Neto SP**, Alvarenga RM, Vasconcelos CC, Alvarenga MP, Pinto LC, Pinto VL. Evaluation of pattern-reversal visual evoked potential in patients with neuromyelitis optica. Mult Scler. 2013;19:173–178.
35. **Ohnari K**, Okada K, Takahashi T, Mafune K, Adachi H. Evoked potentials are useful for diagnosis of neuromyelitis optica spectrum disorder. J Neurol Sci. 2016;364:97–101.
36. **Ringelstein M**, Kleiter I, Ayzenberg I, Borisow N, Paul F, Ruprecht K, Kraemer M, Cohn E, Wildemann B, Jarius S, Hartung HP, Aktas O, Albrecht P. Visual evoked potentials in neuromyelitis optica and its spectrum disorders. Mult Scler. 2014;20:617–620.
37. **Martinelli V**, Comi G. Il valore prognostico dei potenziali evocati nella sclerosi multipla [in Italian]. In: Comi G, ed. I potenziali evocati nella sclerosi multipla: diagnosi, prognosi e monitoraggio: Springer, 1995:105–116.
38. **Onofri M**, Gambi D, Thomas A. Fisiopatologia dei ritardi di conduzione nella sclerosi multipla [in Italian]. In: Comi G, ed. I potenziali evocati nella sclerosi multipla: diagnosi, prognosi e monitoraggio. Berlin, Germany: Springer, 1995:131–149.
39. **Klistorner A**, Arvind H, Garrick R, Yiannikas C, Paine M, Graham SL. Remyelination of optic nerve lesions: spatial and temporal factors. Mult Scler. 2010;16:786–795.
40. **Jenkins TM**, Toosy AT, Ciccarelli O, Miszkiel KA, Wheeler-Kingshott CA, Henderson AP, Kallis C, Mancini L, Plant GT, Miller DH, Thompson AJ. Neuroplasticity predicts outcome of optic neuritis independent of tissue damage. Ann Neurol. 2010;67:99–113.
41. **Lee KH**, Hashimoto SA, Hooge JP, Kastrukoff LF, Oger JJ, Li DK, Paty DW. Magnetic resonance imaging of the head in the diagnosis of multiple sclerosis: a prospective two years follow up with comparison of clinical evaluation, evoked potentials, oligoclonal banding, and CT. Neurology. 1991;41:657–660.
42. **Matthews WB**, Wattam-Bell JR, Pountey E. Evoked potentials in the diagnosis of multiple sclerosis: a follow-up study. J Neurol Neurosurg Psychiatry. 1982;45:303–307.
43. **Hume AL**, Waxman SG. Evoked potentials in suspected multiple sclerosis: diagnostic value and prediction of clinical course. J Neurol Sci. 1988;83:191–210.
44. **Fraser CL**, Klistorner A, Graham S, Garrick R, Billson F, Grigg J. Multifocal visual evoked potential latency analysis: predicting progression to multiple sclerosis. Arch Neurol. 2006;63:847–850.
45. **Klistorner A**, Graham S, Fraser C, Garrick R, Nguyen T, Paine M, O'Day J, Grigg J, Arvind H, Billson FA. Electrophysiological evidence for heterogeneity of lesions in optic neuritis. Invest Ophthalmol Vis Sci. 2007;48:4549–4556.
46. **Samsen P**, Chuenkongkaew WL, Masayaanon P, Chirapapaisan N, Ruangvaravate N, Loket S. A comparative study of visual evoked potentials in optic neuritis and optic neuritis with multiple sclerosis. J Med Assoc Thai. 2007;90:313–318.
47. **Klistorner A**, Arvind H, Nguyen T, Garrick R, Paine M, Graham S, Yiannikas C. Fellow eye changes in optic neuritis correlate with the risk of multiple sclerosis. Mult Scler. 2009;15:928–932.
48. **Alshowaeir D**, Yannikas C, Garrick R, Van Der Walt A, Graham SL, Fraser CL, Klistorner A. Multifocal VEP assessment of optic neuritis evolution. Clin Neurophysiol. 2015;126:1617–1623.
49. **Fuhr P**, Borggrefe-Chappuis A, Schindler C, Kappos L. Visual and motor evoked potentials in the course of multiple sclerosis. Brain. 2001;124:2162–2168.
50. **Kallmann BA**, Fackelmann S, Toyka KV, Rieckmann P, Reiners K. Early abnormalities of evoked potentials and future disability in patients with multiple sclerosis. Mult Scler. 2006;12:58–65.
51. **Jung P**, Beyerle A, Ziemann U. Multimodal evoked potentials measure and predict disability progression in early relapsing–remitting multiple sclerosis. Mult Scler. 2008;14:553–556.
52. **Raz N**, Dotan S, Chokron S, Ben-Hur T, Levin N. Demyelination affects temporal aspects of perception: an optic neuritis study. Ann Neurol. 2012;71:531–538.
53. **Blanco R**, Pérez-Rico C, Puertas-Muñoz I, Ayuso-Peralta L, Boquete L, Arévalo-Serrano J. Functional assessment of the visual pathway with multifocal visual evoked potentials, and their relationship with disability in patients with multiple sclerosis. Mult Scler. 2014;20:183–191.
54. **De Santiago L**, Ortiz del Castillo M, Blanco R, Barea R, Rodríguez-Ascariz JM, Miguel-Jiménez JM, Sánchez-Morla EM, Boquete L. A signal-to-noise-ratio-based analysis of multifocal visual-evoked potentials in multiple sclerosis risk assessment. Clin Neurophysiol. 2016;127:1574–1580.
55. **Aminoff MJ**, Davis SL, Panitch HS. Serial evoked potentials studies in patients with definite multiple sclerosis. Arch Neurol. 1984;41:1197–1202.
56. **Anderson DC**, Slater GE, Sherman R, Ettinger MG. Evoked potentials to test a treatment of chronic multiple sclerosis. Arch Neurol. 1987;44:1232–1236.
57. **Brigell M**, Kaufman DI, Bobak P, Beydoun A. The pattern visual evoked potential. A multicenter study using standardized techniques. Doc Ophthalmol. 1994;86:65–79.
58. **Narayanan D**, Cheng H, Tang RA, Frishman LJ. Reproducibility of multifocal visual evoked potential and traditional visual evoked potential in normal and multiple sclerosis eyes. Doc Ophthalmol. 2015;130:31–41.
59. **You Y**, Klistorner A, Thie J, Graham SL. Latency delay of visual evoked potential is a real measurement of demyelination in a rat model of optic neuritis. Invest Ophthalmol Vis Sci. 2011;52:6911–6918.
60. **Matthews VB**, Small DG. Serial recordings of visual and somatosensory evoked potentials in multiple sclerosis. J Neurol. 1979;40:11–21.
61. **De Weer AW**, Jonkman EJ. Changes in visual and short latency somatosensory evoked potentials in patients with multiple sclerosis. In: Courjon J, Mauguire F, Revol N, eds. Clinical Applications of Evoked Potentials in Neurology. New York, NY: Raven Press, 1987:527–534.
62. **Walsh JC**, Garrick R, Cameron J, McLeod JG. Evoked potentials changes in clinically definite multiple sclerosis: a two year follow up study. J Neurol Neurosurg Psychiatry. 1982;45:494–500.
63. **Ghezzi A**, Zaffaroni M, Caputo D, Montanini R, Cazzullo CL. Evaluation of evoked potentials and lymphocite subsets as possible markers of multiple sclerosis: one year follow-up of 30 patients. J Neuro Neurosurg Psychiatry. 1986;49:913–919.
64. **Aktas O**, Albrecht P, Hartung HP. Optic neuritis as a phase 2 paradigm for neuroprotection therapies of multiple sclerosis: update on current trials and perspectives. Curr Opin Neurol. 2016;29:199–204.
65. **Martínez-Lapiscina EH**, Sanchez-Dalmau B, Fraga-Pumar E, Ortiz-Perez S, Tercero-Uribe AI, Torres-Torres R, Villoslada P. The visual pathway as a model to understand brain damage in multiple sclerosis. Mult Scler. 2014;20:1678–1685.
66. **Martínez-Lapiscina EH**, Fraga-Pumar E, Gabilondo I, Martínez-Heras E, Torres-Torres R, Ortiz-Pérez S, Llufriu S, Tercero A, Andorra M, Roca MF, Lampert E, Zubizarreta I, Saiz A, Sanchez-Dalmau B, Villoslada P. The multiple sclerosis visual pathway cohort: understanding neurodegeneration in MS. BMC Res Notes. 2014;7:910.
67. **Roed HG**, Langkilde A, Sellebjerg F, Lauritzen M, Bang P, Mørup A, Frederiksen JL. A double-blind, randomized trial of IV immunoglobulin treatment in acute optic neuritis. Neurology. 2005;64:804–810.
68. **Tsakiri A**, Kallenbach K, Fuglø D, Wanscher B, Larsson H, Frederiksen J. Simvastatin improves final visual outcome in acute optic neuritis: a randomized study. Mult Scler. 2012;18:72–81.

69. **Cadavid D**, Balcer L, Galetta S, Aktas O, Ziemssen T, Vanopdenbosch L, Frederiksen J, Skeen M, Jaffe GJ, Butzkueven H, Ziemssen F, Massacesi L, Chai Y, Xu L, Freeman S; RENEW Study Investigators. Safety and efficacy of opicinumab in acute optic neuritis (RENEW): a randomised, placebo-controlled, phase 2 trial. Lancet Neurol. 2017;16:189–199.
70. **Sühs KW**, Hein K, Sättler MB, Görlitz A, Ciupka C, Scholz K, Käsmann-Kellner B, Papanagiotou P, Schäffler N, Restemeyer C, Bittersohl D, Hassenstein A, Seitz B, Reith W, Fassbender K, Hilgers R, Heesen C, Bähr M, Diem R. A randomized, double-blind, phase 2 study of erythropoietin in optic neuritis. Ann Neurol. 2012;72:199–210.
71. **Connick P**, Kolappan M, Crawley C, Webber DJ, Patani R, Michell AW, Du MQ, Luan SL, Altmann DR, Thompson AJ, Compston A, Scott MA, Miller DH, Chandran S. Autologous mesenchymal stem cells for the treatment of secondary progressive multiple sclerosis: an open-label phase 2a proof-of-concept study. Lancet Neurol. 2012;11:150–156.
72. **Green AJ**, Gelfand JM, Cree BA, Bevan C, Boscardin WJ, Mei F, Inman J, Arnow S, Devereux M, Abounasr A, Nobuta H, Zhu A, Friessen M, Gerona R, von Büdingen HC, Henry RG, Hauser SL, Chan JR. Clemastine fumarate as a remyelinating therapy for multiple sclerosis (ReBUILD): a randomised, controlled, double-blind, crossover trial. Lancet. 2017;390:2481–2489.
73. **Raftopoulos R**, Hickman SJ, Toosy A, Sharrack B, Mallik S, Paling D, Altmann DR, Yiannakas MC, Malladi P, Sheridan R, Sarrigiannis PG, Hoggard N, Koltzenburg M, Gandini Wheeler-Kingshott CA, Schmierer K, Giovannoni G, Miller DH, Kapoor R. Phenytoin for neuroprotection in patients with acute optic neuritis: a randomised, placebo-controlled, phase 2 trial. Lancet Neurol. 2016;15:259–269.
74. **Cadavid D**, Klistorner A, Chai Y, Leocani L, Aktas O, Butzkueven H, Ziemssen T, Ziemssen F, Frederiksen J, Xu L. Evidence that the anti-LINGO-1 monoclonal antibody BIIB033 protects against multifocal visual evoked potential amplitude loss in the fellow eye of subjects with unilateral acute optic neuritis. ECTRIMS Online Libr. 2015;116697.
75. **Halliday AM**, McDonald WI, Mushin J. Delayed visual evoked response in optic neuritis. Lancet. 1972;1:982–985.
76. **Bynke H**, Rosén I, Sandberg-Wollheim M. Correlation of visual evoked potentials, ophthalmological and neurological findings after unilateral optic neuritis. Acta Ophthalmol (Copenh). 1980;58:673–687.
77. **Laron M**, Cheng H, Zhang B, Schiffman JS, Tang RA, Frishman LJ. Comparison of multifocal visual evoked potential, standard automated perimetry and optical coherence tomography in assessing visual pathway in multiple sclerosis patients. Mult Scler. 2010;16:412–426.
78. **Narayanan D**, Cheng H, Tang RA, Frishman LJ. Longitudinal evaluation of visual function in multiple sclerosis. Optom Vis Sci. 2015;92:976–985.
79. **Seiple W**, Holopigian K, Clemens C, Greenstein VC, Hood DC. The multifocal visual evoked potential: an objective measure of visual fields? Vis Res. 2005;45:1155–1163.
80. **Hood DC**, Odel JG, Zhang X. Tracking the recovery of local optic nerve function after optic neuritis: a multifocal vep study. Invest Ophthalmol Vis Sci. 2000;41:4032–4038.
81. **Hood DC**, Zhang X, Greenstein VC, Kangovi S, Odel JG, Liebmann JM, Ritch R. An interocular comparison of the multifocal vep: a possible technique for detecting local damage to the optic nerve. Invest Ophthalmol Vis Sci. 2000;41:1580–1587.
82. **Pueyo V**, Martin J, Fernandez J, Almarcegui C, Ara J, Egea C, Pablo L, Honrubia F. Axonal loss in the retinal nerve fiber layer in patients with multiple sclerosis. Mult Scler. 2008;14:609–614.
83. **Thurtell MJ**, Bala E, Yaniglos SS, Rucker JC, Peachey NS, Leigh RJ. Evaluation of optic neuropathy in multiple sclerosis using low-contrast visual evoked potentials. Neurology. 2009;73:1849–1857.
84. **Klistorner A**, Arvind H, Nguyen T, Garrick R, Paine M, Graham S, O'Day J, Grigg J, Billson F, Yiannikas C. Axonal loss and myelin in early ON loss in postacute optic neuritis. Ann Neurol. 2008;64:325–331.
85. **Klistorner A**, Arvind H, Nguyen T, Garrick R, Paine M, Graham S, O'Day J, Yiannikas C. Multifocal VEP and OCT in optic neuritis: a topographical study of the structure-function relationship. Doc Ophthalmol. 2009;118:129–137.
86. **Sriram P**, Wang C, Yiannikas C, Garrick R, Barnett M, Parratt J, Graham SL, Arvind H, Klistorner A. Relationship between optical coherence tomography and electrophysiology of the visual pathway in non-optic neuritis eyes of multiple sclerosis patients. PLoS One. 2014;9:e102546.
87. **Gundogan FC**, Demirkaya S, Sobaci G. Is optical coherence tomography really a new biomarker candidate in multiple sclerosis?—a structural and functional evaluation. Invest Ophthalmol Vis Sci. 2007;48:5773–5781.
88. **Parisi V**, Manni G, Spadaro M, Colacino G, Restuccia R, Marchi S, Bucci MG, Pierelli F. Correlation between morphological and functional retinal impairment in multiple sclerosis patients. Invest Ophthalmol Vis Sci. 1999;40:2520–2527.
89. **Klistorner A**, Garrick R, Barnett MH, Graham SL, Arvind H, Sriram P, Yiannikas C. Axonal loss in non-optic neuritis eyes of patients with multiple sclerosis linked to delayed visual evoked potential. Neurology. 2013;80:242–245.
90. **Klistorner A**, Garrick R, Paine M, Graham SL, Arvind H, Van Der Walt A, Tsonis S, Yiannikas C. Relationship between chronic demyelination of the optic nerve and short term axonal loss. J Neurol Neurosurg Psychiatry. 2012;83:311–314.
91. **Henderson AP**, Altmann DR, Trip SA, Miszkiel KA, Schlottmann PG, Jones SJ, Garway-Heath DF, Plant GT, Miller DH. Early factors associated with axonal loss after optic neuritis. Ann Neurol. 2011;70:955–963.
92. **Klistorner A**, Arvind H, Garrick R, Graham SL, Paine M, Yiannikas C. Interrelationship of optical coherence tomography and multifocal visual-evoked potentials after optic neuritis. Invest Ophthalmol Vis Sci. 2010;51:2770–2777.
93. **Leocani L**, Dalla Costa G, Guerrieri S, Pisa M, Zanetta C, Carlucci F, Martinelli V, Comi G. Visual evoked potentials are more sensitive than optical coherence tomography in clinically isolated syndrome. ECTRIMS Online Libr. 2017;200250.
94. **Trip SA**, Wheeler-Kingshott C, Jones SJ, Li WY, Barker GJ, Thompson AJ, Plant GT, Miller DH. Optic nerve diffusion tensor imaging in optic neuritis. Neuroimage. 2006;30:498–505.
95. **Kolbe S**, Chapman C, Nguyen T, Bajraszewski C, Johnston L, Kean M, Mitchell P, Paine M, Butzkueven H, Kilpatrick T, Egan G. Optic nerve diffusion changes and atrophy jointly predict visual dysfunction after optic neuritis. Neuroimage. 2009;45:679–686.
96. **van der Walt A**, Kolbe SC, Wang YE, Klistorner A, Shuey N, Ahmadi G, Paine M, Marriott M, Mitchell P, Egan GF, Butzkueven H, Kilpatrick TJ. Optic nerve diffusion tensor imaging after acute optic neuritis predicts axonal and visual outcomes. PLoS One. 2013;8:e83825.
97. **Thorpe JW**, Barker GJ, Jones SJ, Moseley I, Losseff N, MacManus DG, Webb S, Mortimer C, Plummer DL, Tofts PS. Magnetisation transfer ratios and transverse magnetisation decay curves in optic neuritis: correlation with clinical findings and electrophysiology. J Neurol Neurosurg Psychiatry. 1995;59:487–492.
98. **Hickman SJ**, Toosy AT, Jones SJ, Altmann DR, Miszkiel KA, MacManus DG, Barker GJ, Plant GT, Thompson AJ, Miller DH. Serial magnetization transfer imaging in acute optic neuritis. Brain. 2004;127:692–700.
99. **Inglese M**, Ghezzi A, Bianchi S, Gerevini S, Sormani MP, Martinelli V, Comi G, Filippi M. Irreversible disability and tissue loss in multiple sclerosis: a conventional and magnetization transfer magnetic resonance imaging study of the optic nerves. Arch Neurol. 2002;59:250–255.
100. **Trip SA**, Schlottmann PG, Jones SJ, Li WY, Garway-Heath DF, Thompson AJ, Plant GT, Miller DH. Optic nerve magnetization transfer imaging and measures of axonal

loss and demyelination in optic neuritis. Mult Scler. 2007;13:875–879.
101. **Klistorner A**, Chaganti J, Garrick R, Moffat K, Yiannikas C. Magnetisation transfer ratio in optic neuritis is associated with axonal loss, but not with demyelination. Neuroimage. 2011;56:21–26.
102. **Wang Y**, van der Walt A, Paine M, Klistorner A, Butzkueven H, Egan GF, Kilpatrick TJ, Kolbe SC. Optic nerve magnetisation transfer ratio after acute optic neuritis predicts axonal and visual outcomes. PLoS One. 2012;7:e52291.
103. **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;40:765–770.
104. **van der Walt A**, Kolbe S, Mitchell P, Wang Y, Butzkueven H, Egan G, Yiannikas C, Graham S, Kilpatrick T, Klistorner A. Parallel changes in structural and functional measures of optic nerve myelination after optic neuritis. PLoS One. 2015;10:e0121084.
105. **Alshowaeir D**, Yiannikas C, Garrick R, Parratt J, Barnett MH, Graham SL, Klistorner A. Latency of multifocal visual evoked potentials in nonoptic neuritis eyes of multiple sclerosis patients associated with optic radiation lesions. Invest Ophthalmol Vis Sci. 2014;55:3758–3764.
106. **Kolbe S**, Bajraszewski C, Chapman C, Nguyen T, Mitchell P, Paine M, Butzkueven H, Johnston L, Kilpatrick T, Egan G. Diffusion tensor imaging of the optic radiations after optic neuritis. Hum Brain Mapp. 2012;33:2047–2061.
107. **Kolbe SC**, van der Walt A, Butzkueven H, Klistorner A, Egan GF, Kilpatrick TJ. Serial diffusion tensor imaging of the optic radiations after acute optic Neuritis. J Ophthalmol. 2016;2016:2764538.
108. **Accornero N**, Gregori B, Galié E, De Feo A, Agnesi R. A new color vep procedure discloses asymptomatic visual impairments in optic neuritis and glaucoma suspects. Acta Neurol Scand. 2000;102:258–263.
109. **Sartucci F**, Murri L, Orsini C, Porciatti V. Equiluminant red-green and blue-yellow VEPs in multiple sclerosis. J Clin Neurophysiol. 2001;18:583–591.
110. **Norcia AM**, Appelbaum LG, Ales JM, Cottereau BR, Rossion B. The steady-state visual evoked potential in vision research: a review. J Vis. 2015;15:4.
111. **Frohman AR**, Schnurman Z, Conger A, Conger D, Beh S, Greenberg B, Sutter E, Calabresi PA, Balcer LJ, Frohman TC, Frohman EM. Multifocal visual evoked potentials are influenced by variable contrast stimulation in MS. Neurology. 2012;79:797–801.
112. **Thurtell MJ**, Galetta SL. Low-contrast multifocal visual evoked potentials: identifying more shades of gray in MS. Neurology. 2012;79:732–733.
113. **De Santiago L**, Fernández A, Blanco R, Pérez-Rico C, Rodríguez-Ascariz JM, Barea R, Miguel-Jiménez JM, Amo C, Sánchez-Morla EM, Boquete L. Improved measurement of intersession latency in mfVEPs. Doc Ophthalmol. 2014;129:65–69.
114. **Malmqvist L**, De Santiago L, Fraser C, Klistorner A, Hamann S. Exploring the methods of data analysis in multifocal visual evoked potentials. Doc Ophthalmol. 2016;133:41–48.
115. **De Santiago L**, Klistorner A, Ortiz M, Fernández-Rodríguez AJ, Rodríguez Ascariz JM, Barea R, Miguel-Jiménez JM, Boquete L. Software for analysing multifocal visual evoked potential signal latency progression. Comput Biol Med. 2015;59:134–141.