

## Review article

## The electrophysiological assessment of visual function in Multiple Sclerosis

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## ABSTRACT

The assessment of vision is integral to the diagnosis and monitoring of patients with multiple sclerosis (MS). Visual electrophysiology, previously a critical investigation in patients with suspected MS, has in large part been supplanted by magnetic resonance imaging in clinical routine. However, the development of multi-focal visual evoked potentials and the advent of putative re-myelinating therapies that can be monitored with these techniques has led to a resurgence of interest in the field. Here, we review the clinical applications, technical considerations and limitations of visual evoked potentials in the management of patients with MS.

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## 1. Introduction

Multiple Sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) characterised by focal demyelinating lesions and axonal dysfunction/degeneration that results in variable clinical disability. MS lesions occur throughout the CNS and frequently affect the visual pathways. Optic neuritis (ON), acute inflammation of the optic nerve(s), is the first presenting symptom in up to 1 in 5 people with MS and occurs overtly in 50% of individ-

uals throughout the course of their disease (Hojjati et al., 2015; Miller et al., 2005; Percy et al., 1972). Sub-clinical optic nerve involvement is also common: 40% of individuals with objective evidence of optic nerve damage have no history of symptomatic ON (Kahana et al., 1973). Magnetic resonance imaging (MRI)-detectable lesions in the optic radiation(s) are present in up to 70% of people with MS (Alshowaier et al., 2014; Hornabrook et al., 1992). A predilection for periventricular involvement in MS may explain the prevalence of lesions in the optic radiations, which project from the lateral geniculate nuclei of the thalamus to the primary visual cortex in the occipital lobe, flanking the lateral ventricles. Lesions in the optic radiations, as opposed to the anterior visual pathway, more frequently lead to covert visual dysfunction

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(Plant et al., 1992; Sisto et al., 2005). The largely subclinical nature of visual dysfunction in MS necessitates the use of para-clinical tools in its assessment.

## 2. Visual evoked potentials: MS diagnosis

Historically, visual evoked potentials (VEP) were primarily used to support the diagnosis of MS (Poser et al., 1983) by providing evidence of demyelinating lesions within the CNS. In 1972, delayed VEPs were noted in patients with MS (Halliday et al., 1972), an observation that provided para-clinical evidence of demyelination in patients with insufficient supporting clinical history to fulfil the Poser criteria for definite MS (Matthews et al., 1982; McAlpine et al., 1972). As a diagnostic tool, VEPs have largely been supplanted by MRI, which is more sensitive in detecting cerebral lesions (Filippini et al., 1994). Beer et al. showed that while 29% of patients with a diagnosis of possible MS can be re-classified as definite MS by VEP, some 60% of patients can be reclassified by MRI (Beer et al., 1995). This study compared conventional VEPs with MR imaging performed at 1.5 Tesla field strength; widespread adoption of more sensitive 3 Tesla MRI scanners would likely further widen this difference. However, the frequency of abnormal VEP measures (absent or delayed p100, or significant inter-ocular difference of p100) was 37%, only half the frequency of abnormal VEPs reported in other studies in patients with MS (Filippini et al., 1994; Kupersmith et al., 1983; Sanjari, 2017; Walsh, 2005).

While the advent of MRI has transformed the diagnosis of MS, VEPs provide a slight improvement in the sensitivity of contemporary diagnostic criteria by adding an extra site, the optic nerve, to the dissemination in space (DIS) criteria (Filippi et al., 2018). VEPs were not incorporated into the 2017 MacDonald Criteria, as their inclusion also weakens the specificity of the criteria for multiple sclerosis (Thompson et al., 2018). For example, competing differential diagnoses such as neurosarcoidosis (Oksanen and Salmi, 1986), neuromyelitis optica (Neto et al., 2013; Ringelstein et al., 2014), Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) (Parisi et al., 2000), Behcet's disease (Anlar et al., 2006), adrenoleukodystrophy (Kaplan et al., 1993; Tobimatsu et al., 1985) and neurosyphilis (Conrad et al., 1983) have also been associated with prolonged VEP latency. Therefore, prolongation of VEP latency in isolation provides little additional information to help answer the clinical question: "Does this patient have Multiple Sclerosis?"

Prolonged VEP may aid in differentiating demyelination from microvascular disease in patients with non-specific cerebral lesions (T2 hyperintensities). Conversely, in cases of hemianopia secondary to large vessel infarction, VEPs from the affected visual hemifield demonstrate significantly reduced amplitude, with no latency prolongation, relative to the intact visual hemifield (Yadav and Ciuffreda, 2015).

## 3. Visual evoked potentials: MS monitoring

Despite the absence of VEPs from modern diagnostic criteria for MS, some studies have demonstrated the utility of longitudinal electrophysiological monitoring to assess disease progression. Longitudinal VEP measures in patients with relapsing MS treated with  $\beta$ -interferon (Anlar et al., 2003) and fingolimod (Iodice et al., 2016) have been incorporated into prognostic models that are able to predict future disability by up to 20 years (Schlaeger et al., 2014). VEPs correlate less strongly than motor or sensory evoked potentials with the ubiquitous clinical measure of MS disability, the Expanded Disability Status Scale (EDSS). However, this reflects the emphasis of the EDSS on mobility, particularly at higher levels of disability; as well as its use of a poor measure of visual dysfunction,

namely high contrast letter acuity (Balcer et al., 2000). This dissociation also suggests that whilst interrogation of one neural pathway may correlate loosely with global disease activity and disability, it may not be sufficient for clinical management of individual patients due to the heterogeneity of the disease.

VEPs have also been largely replaced by MRI for monitoring MS disease activity. Despite the clinical-radiological dissociation between disability and MRI lesion burden (Barkhof, 2002), the accrual of new T2 hyperintense lesions is considered to be indicative of ongoing inflammatory activity, and therefore suboptimal disease control. VEPs demonstrate greater sensitivity in detecting damage to the optic nerves than MRI; and patients with prior history of optic neuritis more frequently have delayed or absent VEPs than identifiable optic nerve lesions on MRI (Al-Eajailat and Al-MadaniSenior, 2014; Miller et al., 1988). Nevertheless, extrapolating these benefits to clinical practice is hindered by the lack of specificity of VEP changes, and in particular their inability to distinguish active inflammation from established pathology.

## 4. Pathophysiological insights from VEP

Whilst VEPs have a limited role in clinical decision-making, they provide insights into pathophysiological changes in the visual system in patients with MS. The visual system also provides an ideal 'human model' that is frequently affected by MS lesions and able to be comprehensively and non-invasively interrogated by both visual electrophysiology and MRI.

Prolongation of VEP latency has long been viewed as an indicator of demyelination; and the degree of demyelination within the visual pathway of animal models correlates with the magnitude of delay (You et al., 2017). Shortening of VEP latency is considered to be a biomarker for re-myelination, and on this basis was used as the primary endpoint in clinical trials of the putative promyelinating agents, opicinumab (Cadavid et al., 2017) and clemastine (Green et al., 2017). Spontaneous reduction of VEP latency occurs in the early recovery phase of acute optic neuritis (Rinalduzzi et al., 2001). This period corresponds with the extensive, although not always complete, re-myelination, demonstrated by post-mortem series to occur weeks to months after the demyelinating event (Prineas et al., 1993). Furthermore, the post-chiasmatic optic radiation lesion burden correlates with the degree of VEP latency prolongation (Alshowaier et al., 2014), indicating that visual pathway pathology extrinsic to the optic nerve(s) also impacts the VEP.

Despite our understanding of the effect of demyelination on VEPs, the symptomatology of demyelination is less well defined. Conduction block of demyelinated axons in an inflammatory milieu (Smith, 1994), and axonal degeneration leads to loss of neural transmission and clinical deficits. Conduction block can be experimentally induced in patients with hyperthermia, however this does not result in a prolonged VEP latency despite causing a decline in visual function (Matthews et al., 1979). The converse is also true, as individuals with prolonged VEP latency frequently may have no visual dysfunction, as measured by contrast sensitivity (Shandiz et al., 2010). As demyelination and axonal loss frequently co-occur within new lesions (Trapp et al., 1998), it is difficult to dissociate the clinical effect of the two pathological processes.

VEP amplitude is considered to be a biomarker of axonal integrity (You et al., 2012) or function and correlates with visual recovery in patients following optic neuritis (Halliday et al., 1977; Hickman et al., 2004; Longbrake et al., 2016). This contrasts with latency measures, which remain delayed despite the improvement of VEP amplitude and visual acuity (Youl et al., 1991). Amplitude recovery following acute optic neuritis is primarily due to the reversal of conduction block in demyelinated axons (Halliday and

McDonald, 1977). The utilisation of a greater volume of visual cortex to process the signal has also been implicated as an additional contributor to improved amplitude in this context (Werring et al., 2000). The activated volume of visual cortical regions is lower when stimulating the affected eyes of ON patients compared to the unaffected eye (Gareau et al., 1999) and healthy controls (Anwar et al., 2009). In addition to functional MRI metrics, micro-structural MRI measures correlate with VEP amplitudes. VEP amplitude in patients with a history of ON has been demonstrated to inversely correlate with MRI mean diffusivity (MD) of the optic nerve (Trip et al., 2006). MD can be correlated with axonal integrity (when variables such as oedema are excluded); the more destructive a lesion is, the greater the MD (Horsfield and Jones, 2002). This relationship with MRI-derived MD underscores the role of VEP amplitude as a functional marker of axonal integrity.

### 5. Impact of visual cortex on the VEP

Whilst axonal dysfunction and loss underlies clinical disability (Frederiksen and Petrera, 1999), the reliability of VEP amplitude measurements is poor. Inter-subject variability in VEPs led early authors to suggest that there is no standard waveform to describe the VEP (Werre and Smith, 1964). Although a standard VEP waveform is now accepted for each VEP technique (Odom et al., 2016), the significant inter-subject variability in VEP amplitude (Ciganek, 1969; Shors et al., 1986; Werre and Smith, 1964) and somewhat lesser degree of intra-subject variability (Fagan et al., 1984) largely restricts the clinical use of amplitude measures to the assessment of inter-ocular differences. The cause of the large amplitude variance stems from inter-subject differences in skull thickness (Hagemann et al., 2008; Myslobodsky et al., 1989) and cortical folding of the primary visual cortex (Sulejmanpasic and Drnda, 2017) (Fig. 1). The heterogeneity of visual cortical topography is large, with differences in total striate and the striate cortex on the outer surface of the brain reaching 3-fold and 4-fold, respectively, in a post-mortem series (Stensaas et al., 1974). Routine EEG studies have demonstrated that the size of the signal recorded on the scalp is dependent on the size and location of the cortical region involved in generating the potential (Ramantani et al., 2016). This cortical variance may underlie the amplitude asymmetries seen, with greater amplitude recorded after stimulation of the right visual hemifield (Abe and Kuroiwa, 1990; Kuroiwa et al., 1987; Pike and Polich, 1988), whose corresponding left striate cortex is more exposed than the right visual cortex (Stensaas et al., 1974). However, the same inference does not hold for the upper visual hemifield, which is associated with a lower VEP amplitude compared to the lower hemifield (Fortune and Hood, 2003), despite greater exposure of the striate cortex below than above the calcarine sulcus (Stensaas et al., 1974).

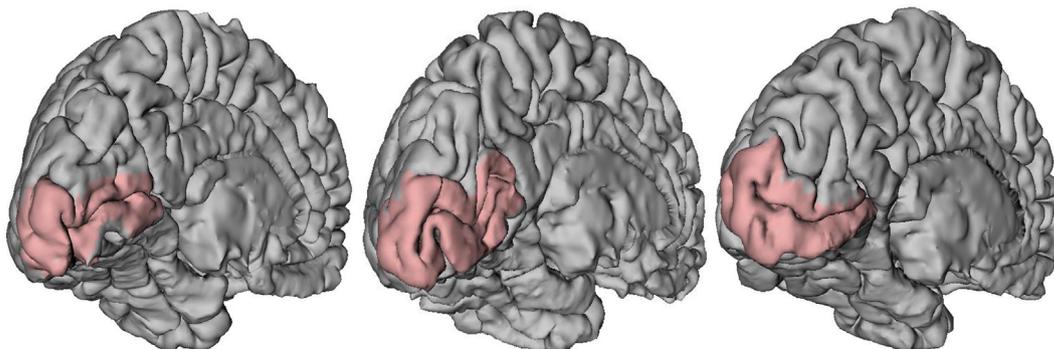
### 6. Conventional VEP acquisition: considerations

The method used to stimulate the VEP influences the waveform properties of the recorded electrical potential. Flash VEP provides a diffuse pan-retinal stimulus allowing the study to be performed without foveal fixation. This allows examination of visual function in individuals in whom pattern-reversal VEPs are unable to be performed due to poor central vision or difficulty maintaining visual fixation due to fatigue or poor test compliance. Pattern-reversal VEP requires visual fixation to maintain the stable projection of the alternating pattern on the retina and focus to minimise blur and reduced pattern contrast. Flash VEPs have significant inter-individual variance and do not distinguish pathology and normal physiology as well as pattern-reversal VEPs (El-Shazly, 2016). However, normal subjects have minimal inter-ocular and inter-hemispheric asymmetry and flash VEP can therefore be used to compare between the eyes of an individual (Holder, 2004). The waveforms acquired with flash VEPs have relatively prolonged peak latencies and reduced amplitudes compared to pattern reversal VEPs (Odom et al., 2016). Prolonged VEP latencies are also recorded when lower contrast stimuli are presented (van der Tweel et al., 1979). Unfortunately, as technological advances have made measuring VEPs possible to a greater number of clinicians and researchers, the computer monitors used to stimulate the visual field produce slower and more varied evoked potentials compared to mechanical shutters (Elze, 2010). This discrepancy is due to lag between the first and last pixel being drawn which results in a dispersed presentation and a relatively delayed VEP (Nagel et al., 2018).

The rate at which stimuli are presented influences the recorded VEP latency. High frequency stimulation results in stimuli being presented during the refractory period, and therefore results in delayed processing (Mitchell et al., 1983). Although visual temporal sensitivity is impaired in patients with prior ON or MS on measures such as critical flicker fusion (Daley et al., 1979), the magnitude of the VEP refractory period is not systematically altered in MS, and therefore does not help differentiate individuals with MS from healthy controls (Mitchell et al., 1983; Skuse and Burke, 1986).

Reducing the luminance of stimuli also results in a delay in the VEP signal. The simultaneous recording of electroretinograms (ERGs) can localise this VEP delay to the retina, with a subsequent normal retino-cortical time (Froehlich and Kaufman, 1991). As MS-associated visual deficits are primarily due to disease in the retino-cortical pathway, rather than in the eye itself, modulation of the luminance of VEP stimuli is unlikely to be of clinical interest in MS.

The susceptibility of VEPs to the aforementioned variables necessitates the need for rigorous standards to be kept when recording VEPs, prompting the International Society for Clinical



**Fig. 1.** Left hemispheric cortical surface of 3 individuals with the visual cortex highlighted in pink (V1 segregated with Freesurfer software<sup>86</sup>). Note the variation in cortical folding around the Calcarine fissure demarcating the upper and lower visual hemifields.

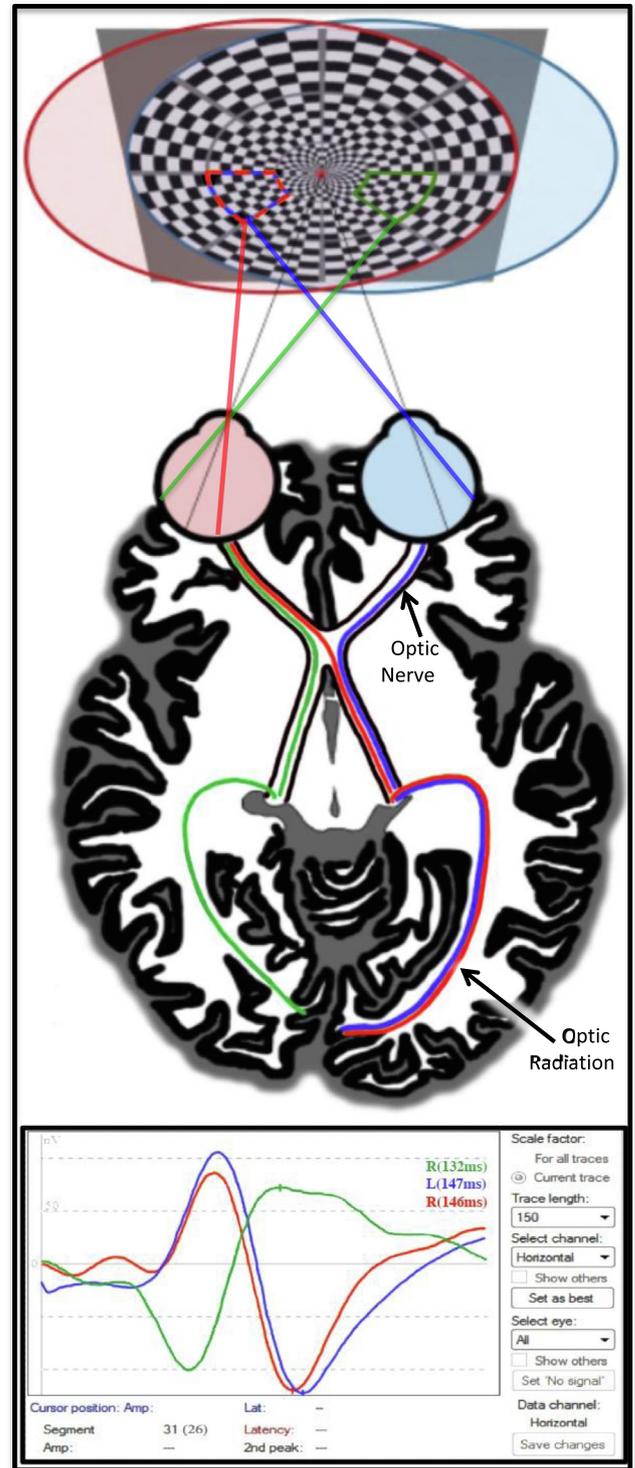
Electrophysiology of Vision (ISCEV) to create guidelines for VEP acquisition (Odom et al., 2016).

## 7. The advent of multifocal VEPs

The folding of the primary visual cortex results in cortical regions corresponding to adjacent sectors of the visual field potentially having opposite orientations and therefore generating inverse potentials (see Fig. 2). Conventional VEPs generate a waveform representative of the entire visual field stimulated, which is the summation of all produced dipoles. This summation results in phase cancellation of dipoles oriented in opposite directions and subsequent loss of potentially clinically relevant information. A recent advance in VEP technology has been the development of the multifocal VEPs (Baseler et al., 1994; Sutter, 1991). This technique utilises a pseudorandom sequence to present stimuli to up to 60 sectors of the tested visual field in a pseudo-independent manner (see Fig. 3). The advantage of recording independent VEPs from different parts of the visual field is that the electrical dipoles generated by the corresponding cortical regions do not cancel each other out (Klistorner et al., 1998). Stimulating the visual field in such a fragmented fashion enhances the sensitivity to all regions evaluated and allows detection of smaller deficits, which may be missed by both the patient and by conventional VEPs (Chan et al., 2005; Nebbioso et al., 2013). The Phase 2 study of opicinumab (RENEW) study demonstrated mfVEPs superiority over conventional VEPs, by more readily detecting treatment-associated conduction changes in eyes recently affected by ON. Moreover, conduction changes occurring in non-ON eyes were detected with mfVEPs, but not conventional VEPs (Klistorner et al., 2018). As a result, mfVEPs have been selected as the primary outcome measure for another study currently assessing the remyelination potential of nanocrystalline gold (Nanocrystalline Gold to Treat Remyelination Failure in Chronic Optic Neuropathy In Multiple Sclerosis (VISIONARY-MS) ClinicalTrials.gov NCT03536559, 2018). Although mfVEPs are more sensitive than conventional VEPs, they also require more time (approximately 5–10 fold) to be performed and this can sometimes be overly demanding for patients with MS associated fatigue.

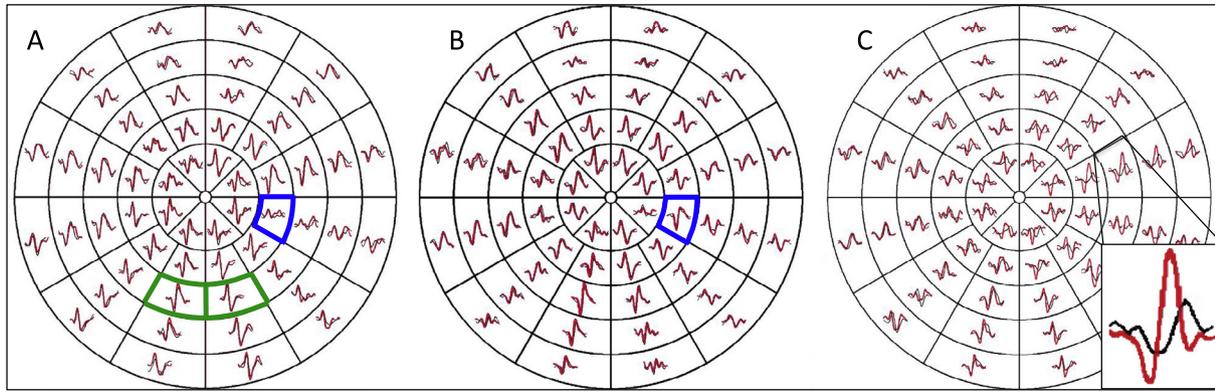
Small defects in the visual field due to anterior visual pathway disease are readily detected by mfVEP, as information from both eyes corresponding to same region in visual space are processed by the same cortical region and therefore have comparable waveforms. Differences in the waveforms between the eyes are therefore considered to reflect pathology in one eye. A caveat to this assumed equivalence is the effect that retinal distance from the optic nerve head has on VEP latency (Shimada et al., 2005). The latency of nasal VEPs are delayed compared to VEPs sampled from the temporal visual hemifield of healthy controls (Hood et al., 2000). This latency disparity likely reflects the time taken for the neural impulse to travel from the retinal area where the signal originated, through the un-myelinated portion of the ganglion cell axon, to the optic nerve head, where the axons become myelinated and saltatory conduction begins. The delay in the neural signal reaching the optic nerve is illustrated by the optic nerve head component (ONHC) seen in multifocal ERGs (Sutter and Bearse, 1999). The retinal components of each ERG waveform occurs at the same time after the visual stimulus, however the delay of the ONHC of each retinal patch corresponds to the distance of that retinal patch to the optic disc, ranging up to 7msec between patches of the same retinal eccentricity. The physiological inter-ocular latency difference needs to be accounted for when comparing waveforms of small sectors in the assessment of sub-clinical visual defects.

The assessment of post-chiasmatic lesions in the optic radiations is dependent on the comparison of the VEP with a “normal” waveform. As intra-subject comparator waveforms are processed



**Fig. 2.** Multifocal Visual Evoked Potential Sectors of the monocular visual field are independently stimulated by reversal of a checkerboard pattern in a pseudo-random sequence. Waveforms acquired from the same sector (blue and yellow sectors) are similar between eyes, as the cortical region generating the VEP signal is the same. A small delay is frequently observed in the signal of the nasal fields (blue) compared to the temporal fields (yellow), representing a longer path through the unmyelinated retina. VEP waveforms from the opposite hemi-field are frequently of opposite polarity (green). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

by different cortical areas, the waveforms will be distinct and not directly comparable. In this scenario, a healthy control database is required to provide the ‘normal’ latency and amplitude ranges



**Fig. 3.** mfVEPs from 2 healthy subjects (A&B). Note the inter-ocular similarity (black trace = right eye, red trace = left eye) within individuals and the variation seen between healthy subjects at the same visual space (blue sectors). The reversal of dipoles due to cortical folding can often be seen across the horizontal and vertical meridians (green sectors). A mfVEP from an individual with a history of right-sided optic neuritis (C) demonstrates delayed latency and reduced amplitude in the right eye compared to the left (insert).

to which the subject's sectorial values are compared (Alshowaeir et al., 2015). Assessment of the post-chiasmatic visual pathway can be enhanced with MRI tractography, providing a length measure to convert VEP latency metrics to a relative conduction velocity (Wang et al., 2017).

### 8. Additional electrophysiological techniques

Electroretinograms (ERGs) also measure the electrical activity of the visual pathway, however the signal is isolated to the anterior pathway between the photoreceptors and the point of ganglion cell myelination at the optic nerve head. Whilst MS is considered to affect the visual pathway from the optic nerve to the visual cortex, ERGs are frequently abnormal with reduced amplitude in individuals with MS (Janáky et al., 2017). This finding has been attributed to retrograde axonal degeneration from optic neuritis or even optic radiation lesions that lead to retinal thinning (Klistorner et al., 2014) and loss of the source of electric potential generating cells. The corollary is also true that, retinal diseases, such as retinitis pigmentosa, not affecting the ganglion cells (Mazzoni et al., 2008), result in significant VEP latency delays as well as lower amplitudes (Hood et al., 2006).

Given their non-specificity to MS and the additional time and specialised equipment required to perform them, ERGs are of no clinical benefit in routine management of MS.

### 9. Conclusions

As radiological and serological para-clinical tests involved in the diagnosis and management of MS advance, visual electrophysiology must adapt to remain clinically relevant. The development of increasingly sophisticated techniques provides an opportunity to detect smaller and less profound visual changes, however the effect of comorbidities and the inherent physiological variation in visual electrophysiology must be recognised to avoid erroneous clinical conclusions. VEPs are providing primary outcomes for the assessment of demyelination and pharmacotherapy-assisted remyelination in Phase 2 MS clinical trials. Ultimately, visual electrophysiology may therefore prove to be a critical tool for neurologists in assessing response to these therapies in clinical practice.

### Declaration of Competing Interest

Dr Barton has received educational support from Biogen, Novartis, Sanofi-Genzyme, Merck Serono and Teva.

Dr Garber has received educational and fellowship support from Merck Serono, Sanofi-Genzyme and Teva.

Dr Klistorner is an inventor on two patents related to mfvep technology, which are held by university of Sydney.

Dr Barnett has received institutional support for research, speaking and/or participation in advisory boards for Biogen, Merck, Novartis, Roche and Sanofi Genzyme. He is a consulting neurologist for RxMx/Medical Safety Systems and research director for the Sydney Neuroimaging Analysis Centre.

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