Comparison of multifocal visual evoked potential, automated perimetry, optical coherence tomography and optic nerve MRI in assessing visual pathway in Egyptian multiple sclerosis patients

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Abstract: Background: Multifocal visual evoked potentials (mfVEP) measure local response amplitude and latency in the field of vision **Objective:** To compare the sensitivity of mfVEP, Humphrey visual field (HVF), optical coherence tomography (OCT) and MRI optic nerve in detecting visual abnormality in multiple sclerosis (MS) patients. **Methods:** MfVEP, HVF, OCT (retinal nerve fiber layer [RNFL]) and MRI optic nerve were performed in 25 MS-ON eyes (last optic neuritis (ON) attack ≥ 6 months prior) and 25 MS-Non-ON eyes without ON history. Criteria to define an eye as abnormal were: mfVEP) amplitude/latency: either amplitude or latency probability plots meeting cluster criteria with 95% specificity) amplitude or latency alone (specificity: 97% and 98%, respectively); HVF, OCT, mean deviation and RNFL thickness meeting $p < 0.05$, respectively. **Results:** MfVEP (amplitude/latency) identified more abnormality in MS-ON eyes (95%) than HVF (72%), OCT (62%), mfVEP amplitude (66%) or latency (67%) alone. 20% of MS-non-ON eyes were abnormal for both mfVEP (amplitude/latency) and HVF compared to 8% with OCT. Agreement between tests ranged from 60% to 80%. MfVEP (amplitude/latency) categorized an additional 20% of MS-ON eyes as abnormal compared to HVF and OCT combined. **Conclusions:** MfVEP, which detects both demyelination (increased latency) and neural degeneration (reduced amplitude) revealed more abnormality than HVF, OCT and MRI optic nerve in MS patients.

Keywords: Comparison; multifocal visual; potential; automated perimetry; optical coherence tomography; optic nerve; MRI; visual pathway; Egyptian; multiple sclerosis; patient

1. Introduction:

Multiple sclerosis (MS) is a common immune-mediated progressive neurodegenerative disease of the CNS that typically manifests with periods of disease activity followed by intervals of remission. MS affects more than 2 million individuals around the globe and more than 500,000 people in the USA [1]. In Egypt there is about 20,000 to 30,000 MS patients according to the report of the Egyptian MS society.

MS remains a significant cause of neurologic disability in young adults and places a heavy medical, psychological and financial burden on human society [2].

Pathology affecting the anterior visual pathway, in particular optic neuritis (ON), is prevalent in MS patients, and is often the initial manifestation of the disease. The retinal nerve fiber layer (RNFL) which consists of unmyelinated axons of retinal ganglion cells that become myelinated past the lamina cribrosa and form the optic nerve, can be visualized using retinal imaging techniques. The RNFL will show retrograde degeneration following damage to the optic nerve or the optic tract in the brain. The eye therefore provides a window for assessing quantitatively, axonal damage associated with ON [3].

Both structural and functional tests can be used to assess damage to the axons of the optic nerve. For structural evaluation, optical coherence tomography (OCT) is a relatively recent optical imaging technique that measures cross-sectional RNFL thickness [4].

Functional testing can be subjective or objective. Standard Automated Perimetry (SAP), such as the Humphrey Visual Field (HVF) test, provides a subjective measure of visual function [5].

The multifocal visual evoked potential (mfVEP) is a relatively new objective approach for assessing early visual pathway integrity. [6].

2. Participants and methods:

In order to compare the sensitivity of the mfVEP in detecting abnormalities in the visual pathway of MS patients with that provided by standard automated

perimetry, using HVF testing, and imaging of the nerve fiber layer, using OCT, or MRI of optic nerve, this study was conducted on 50 multiple sclerosis patients and grouped into 2 equal groups. Each group included 25 patients, group A included 25 patients suffering from optic neuritis as diagnosed by standard automated perimetry and group B included 25 patients were free.

Exclusion criteria:

1. Any progressive neurological disorder (other than MS).;

2. Any state of immunosuppression different from MS;

3. Any ophthalmological causes for retinal damage different from MS;

4. Current or previous treatment with a drug involved in toxic neuropathy;

5. Recent history of acute optic neuritis (<6 months). Patients with ON can be recruited after 6 months of the acute episode;

6. Previous diagnosis of Diabetes Mellitus;

7. Inability to undergo MRI and

8. History of substance abuse in the last 5 years including alcoholism.

I.

II. Methods:

All the patients underwent full neurological and ophthalmic examination, including:

- Best corrected visual acuity (BCVA)
- Biomicroscopy
- Ocular fundus examination after pharmacologically pupil dilatation

The Snellen visual acuity equivalent was determined by the lowest line read on the 100% chart.

Optical Coherence Tomography:

An important exclusion criteria of the patients after the ophthalmic examination was the presence of nystagmus, which can have an important effect on visual fixation (an essential component in obtaining high-quality OCT scans).

Retinal imaging was performed with spectral-domain Cirrus HD-OCT [7]. Briefly, peripapillary and macular scans were obtained with the Optic Disc Cube 200 × 200 and Macular Cube 512 × 128 protocols, respectively. Scans with signal strength less than 7/10 or with artifact were excluded, in accordance with the OSCAR-1B criteria [8].

The retinal nerve fiber layer (RNFL) measurements were obtained after 3 consecutive scans centered on the optic nerve head. OCT software Cirrus, Carl Zeiss Meditec generated a mean RNFL thickness measurement for 360 degrees around the optic disc, four retinal quadrants and 12 clock for our segment (30 degrees for each hour position). All scans were performed without pupil dilatation [9].

Multifocal Visual-Evoked Potential Recordings and Analysis:

The mfVEP recordings were obtained using RETI Scan software 5.9 (Electro-Diagnostic Imaging, Germany). The stimulus was a scaled dartboard with a diameter of 44.5°, containing 60 sectors, each with 16 alternating checks, 8 white (luminance: 200 cd/m2) and 8 black (luminance: <3 cd/m2), with a Michelson contrast of approximately 99%. The sectors were cortically scaled with eccentricity to stimulate approximately equal areas of the visual cortex [10]. The dartboard pattern reversed according to a pseudorandom m-sequence at a frame rate of 75 [11].

Three channels of continuous VEP recordings were obtained with gold cup electrodes. For the midline channel, the electrodes were placed 4 cm above the inion (active), at the inion (reference), and on the forehead (ground). For the other two channels, the same ground and reference electrodes were used, but the active electrodes were placed 1 cm above and 4 cm lateral to the inion on either side. By taking the difference between pairs of channels, three additional "derived" channels were obtained. The records were amplified with the high- and low-frequency cutoffs set at 3 and 100 Hz, respectively, and sampled at 1200 Hz (every 0.83 ms). The impedance was less than 5 K for all subjects. In a single session, two 7-minute recordings were obtained from monocular stimulation of each eye and were averaged for analysis. Second-order kernel best-channel responses were then extracted [12].

This averaging, as well as all other analyses, was computed with custom-made programs written in commercial software [13]. Response amplitudes were calculated by obtaining the root mean square (RMS) of the amplitude for each mfVEP response over time intervals from 45 to 150 ms. Signal-to-noise ratios were calculated for each response by dividing the RMS of the signal window by the average of the 60 RMS values of the noise-only window.

Monocular latencies were measured as the temporal shift producing the best cross-correlation value between the corresponding responses of the patient's eye and a template based on control eyes (monocular analysis) or between the corresponding responses from two eyes (interocular analysis). The latency probability plots were color-coded in a manner similar to the amplitude plots using ovals instead of squares.

III. Statistical Analysis:

Patients' data were tabulated and processed using SPSS (17.0) statistical package for Windows.

- Quantitative variables were expressed by means and standard deviation and were analyzed using student's unpaired t-test. Mann Whitney Willcoxon U

test was used instead of unpaired t-test in non-parametric data (SD>50% mean).

- Qualitative data will be expressed by frequency and percent and were analyzed using Chi-square.

- The sensitivity (the proportion of patients for whom the outcome is positive that are correctly identified) and the specificity (the proportion of patients for whom the outcome is negative that are correctly identified), together with the positive predictive value (the probability that a patient has a positive outcome given that they have a positive test result) and similarly, the negative predictive value (the probability that a patient has a negative outcome given that they have a negative test result) are calculated.

P value >0.05 → insignificant
P value <0.05 → significant
P value <0.01 → highly significant

3. Results:

On comparison of Age, Age of onset, Sex and Marital Status among studied groups were found statistically insignificant.

Global measurements of OCT, HVF, mfVEP and MRI for the MS-ON and MS-no-ON groups:

The averaged retinal nerve fiber layer (RNFL) thickness measured by OCT, MD measured by HVF, and response amplitude (calculated as log SNR) and latency measured by mfVEP are shown for the MS-ON (n = 25) and MS-no-ON (n = 25) groups in. For all parameters there were statistically significant differences between the MS-ON group and the MS-no-ON group with $p < 0.0001$ for RNFL thickness, $p = 0.0005$ for MD, $p < 0.0001$ for mfVEP response amplitude, and $p = 0.0002$ for mfVEP latency (Student's t-test).

MfVEP (amplitude/latency) identified more abnormality in MS-ON eyes (95%) than HVF (72%), OCT (62%), mfVEP amplitude (66%) or latency (67%) alone. 20% of MS-non-ON eyes were abnormal for both mfVEP (amplitude/latency) and HVF compared to 7% with OCT. Agreement between tests ranged from 60% to 80%. MfVEP (amplitude/latency) categorized an additional 15% of MS-ON eyes as abnormal compared to HVF and OCT combined.

4. Discussion:

Mf-VEP is an intriguing new research methods for exploring the intricacies of the visual pathway in ON and MS in that it, in most trials, provides a higher sensitivity and specificity than established methods in monitoring the functional capacity of different regions in the pathway.

Both structural and functional tests can be used to assess damage to the axons of the optic nerve. For structural evaluation, optical coherence tomography (OCT) is a relatively recent optical imaging technique that measures cross-sectional RNFL thickness with high resolution (8–10 microns for Stratus OCT 3000 used in this study) and good reproducibility [23] is easy to perform, time-efficient, and is less costly than magnetic resonance imaging (MRI), a standard evaluative approach in MS patients. OCT has shown promise as a potential surrogate measure of axonal loss and neuro-protection in MS [14].

Functional testing can be subjective or objective. Standard automated perimetry (SAP), such as the Humphrey visual field (HVF) test, provides a subjective measure of visual function that is considered to be a clinical "gold standard" for documenting loss of sensitivity. The visual loss documented by the HVF test in various optic nerve diseases is correlated, to a greater or lesser extent depending upon the study and patient population being assessed, with results from imaging approaches such as OCT [15].

The multifocal visual evoked potential (mfVEP) is a relatively new objective approach for assessing early visual pathway integrity. This noninvasive electrodiagnostic technique records many (typically 60) local visual evoked responses simultaneously from over 40 degree field of vision. In addition to providing response amplitudes, the mfVEP also provides information about nerve conduction velocity (latency) which is useful for assessing the extent of demyelination. The mfVEP has been shown to have good repeatability, even slightly better than that of the HVF in some cases [16], and it detects local defects which would not be possible to find using the traditional VEP which tests global function over a large central region of the visual field [17].

Superior sensitivity and specificity of mf-VEP is shown particularly in revealing small, peripheral lesions in the upper visual field.

Mf-VEP may increase diagnostic sensitivity in ON and abnormal mf-VEP responses from the fellow non-ON afflicted eye may serve as a predictor of MS risk in ON patients.

For example, one study reported that the mfVEP detected 20% more local abnormalities in the visual field than the HVF in patients with ON [18]. Another advantage of the mfVEP is its potential to detect subclinical demyelination, indicated by prolonged latencies in local areas. Prolonged latencies could indicate increased risk of clinically definite MS in a patient with clinically isolated syndrome who has presented only with ON [19,6], compared results from OCT and mfVEP in patients with unilateral ON and found that the mfVEP detected more abnormality than the OCT RNFL thickness in both affected eyes and fellow eyes [20].

[21] observed a significant agreement between mfVEP amplitude and Humphrey perimetry /OCT in MS-ON eyes, and between mfVEP amplitude and OCT in MS but non-ON eyes. They also found significant differences in EDSS score between patients with abnormal and normal mfVEP amplitudes. Abnormal mfVEP amplitude defects (from interocular and monocular probability analysis) were found in 67.9% and 73.7% of the MS-ON and MS-non-ON group eyes, respectively. Delayed mfVEP latencies (interocular and monocular probability analysis) were seen in 70.3% and 73.7% of the MS-ON and MS-non-ON groups, respectively.

In agreement with the previous reports [2,6,22], we found that mfVEP detected more abnormalities in MS patients than the structural test. Such a result is expected because (1) as noted above, the mfVEP or VEP, by virtue of the latency measurements detects demyelination while the OCT does not; (2) the OCT measurement is limited to the anterior visual pathway assessed at the retinal level whereas the functional tests measure integrity of both anterior and posterior visual pathways. According to the Optic Neuritis Treatment Trial, optic neuritis is retrobulbar in approximately two thirds of patients [23]. The OCT will not detect or underestimate the defects when retrograde axonal degeneration is partial or not significant, and is not expected to detect lesions beyond the lateral geniculate nucleus because these are unlikely to lead to retrograde axonal degeneration in the adult retina.

At present, both the HVF and OCT tests (and tradition VEP) are used during ophthalmic evaluation of MS/ON patients, whereas the mfVEP is relatively time consuming and not readily available in most clinics. Compared to the HVF, the mfVEP has the advantage that it is an objective test of local visual function that does not require patients to make a decision. Some MS patients, especially those with advanced disease, may suffer from cognitive impairment [24], and have slowed reaction time, which adversely affects their performance on the HVF test.

Most importantly, the mfVEP also provides local information about delayed responses (latencies), which is not reflected by OCT. The latency information is of high value in MS patients, since a hallmark of the disease is nerve demyelination, which disrupts and slows signal conduction. While most cases of ON can be diagnosed clinically, the detection of subclinical demyelination substantially relies on latency measurements.

[6], reported a strong topographical association between RNFLT and mfVEP amplitude in eyes affected by ON. [34] reported that mfVEP shows greater sensitivity than OCT and Humphrey visual field (HVF) in detecting abnormalities in both an ON eye and its fellow. Even more, prolonged latencies could indicate increased risk of clinically definite MS in a patient with CIS who has presented with only ON [25].

A unique benefit of the mfVEP is its ability to expose a subclinical lesion in the clinically unaffected eyes in MS, not detected with structural and psychophysical diagnostic techniques. [22] demonstrated that the mfVEP was more sensitive in detecting abnormality than the HVF and OCT in both affected and unaffected eyes of MS patients with an ON history and in MS patients with no clinical history of ON in either eye. This result is expected because mfVEP, by virtue of the latency measurements, detects demyelination, whereas OCT does not.

Preliminary studies have indicated that abnormal mf-VEP responses in the fellow, non-ON afflicted eye may serve as a predictor of MS risk in ON patients. This finding naturally must be confirmed. Abnormal mf-VEP response of the fellow eye may reflect both optic nerve involvement as well as retrogeniculate lesions [26].

Furthermore, mf-VEP may increase the diagnostic sensitivity in ON in that latency findings, in preliminary findings, seem to distinguish ON from other optic neuropathies [27].

Compared to the ff-VEP the mf-VEP, in most studies, has shown superior sensitivity and specificity and especially small, peripheral lesions or lesions of the upper visual field seemed to be more readily detected on mf-VEP. In fact, only one study, employing the Metrovision™ system, showed superior sensitivity of the ff-VEP to mf-VEP [28]. As indicated the ff-VEP focuses particularly on the contribution of the central nerve fibres and produces a single global response biased toward the macular region due to cortical overrepresentation. Responses from abnormal and normal regions of the visual field are summed and in many cases the global response is dominated by the lower visual field [29]. The mf-VEP on the other hand represents separate responses from different regions of the visual field by employing different, independent stimuli across the visual field and by combining the sequence of these stimuli with a continuous EEG signal [29].

Furthermore, in some studies in particular when correlating mf-VEP to structural damage (atrophy), amplitude measurements may provide a more suitable parameter. Preliminary trials have thus focused on the ability of mf-VEP amplitude to disclose the degree of axonal damage and mf-VEP latency the degree of regional de- and remyelination. Mf-VEP measures have in this regard been included as a secondary endpoint in newer remyelinating therapies such as anti-LINGO-1 drugs [30]. Thus, both amplitude and

latency parameters seem to add value to the evaluation of the visual system in demyelinating disorders.

Significant limitations exist with regards to the broad utilization of mf-VEP. Even in the hands of the most skillful of technicians the mf-VEP has significant limitations. Uncorrected refractive errors and obscuration of the visual field by ptotic eyelids are known sources of error in general visual testing that also affect mf-VEP [31]. Even when correcting refractive errors, difficulties may remain in interpreting the results of highly myopic patients thus normative databases may need to be created seperatively for these patients [32]. A minority of patients may present difficulties in cooperating and may fall asleep during the examination. Furthermore, in a subset of patients responses obtained from mf-VEP measurements may be dominated by alpha-waves and muscle tension in the vicinity of electrodes [33].

As would be expected, the mfVEP is subject to some inter-individual variability. This naturally complicates statistical evaluation of abnormal and normal responses. A primary reason for the variation has been proposed to be differential cortical folding of the primary visual cortex with associated differences in relationship to the anatomical landmarks used in obtaining the results i.e. the external occipital protuberance [34]. Accordingly, no consensus exists on the placement of electrodes. The primary method to minimize the inter-individual variability in mf-VEP studies has been to include inter-ocular analysis at least in the case of unilateral affliction. The value of choosing the right method in mf-VEP data analysis as an additional factor to decrease intra- and inter-individual variability has also been explored [35].

Further, a common source of error in ff-VEP and HVF, i.e. eccentric fixation of gaze, is also encountered in mf-VEP and may produce false positive field deficits [31].

In the future different stimuli [36,37], or improvements of the interpretation of normal and abnormal responses and improvement of intersession variability by adjustment of software algorithms for obtaining normal and abnormal responses, may improve time consumption and sensitivity of the mf-VEP [38], and explorations of these algorithms in amplitude signal analysis have shown to improve the assessment of patient at risk of developing MS [27].

Thus software parameters should be further investigated in order to improve the diagnostic and prognostic sensitivity of mf-VEP in future.

Conclusion:
The mfVEP, HVF, OCT and MRI optic nerve provide complementary information in detecting visual pathway abnormalities in MS. These tests together identified abnormality in 98% of the MS-ON

eyes. The functional tests provide both objective (mfVEP) and subjective (HVF) information on axonal pathology; the structural test (OCT and MRI) is a valuable tool for documenting axonal loss. The mfVEP latency measure is particularly useful for detection of demyelination in visual pathways which can be subclinical is some cases. Results of both structural and functional tests should be included in longitudinal studies in order to understand the processes involved in the neuronal damage in MS that occurs over time, the repair mechanisms and whether/how therapeutic treatments affect these processes. Further improvements in the mfVEP technique such as the use of sparse stimulation may improve mfVEP SNR and shorten the recording time, and make it more applicable with respect to both amplitude and latency measurements in the clinic setting.

References:
1. Borazanci A.B.; Et al. Multiple Sclerosis: Clinical Features, Pathophysiology, Neuroimaging, and Future Therapies, Future Neurology. 2009; 4(2):229-246.
2. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol. 2010;50:121–127.
3. Beck RW, Trobe JD, Moke PS, Gal RL, Xing D, Bhatti MT, et al. High- and low-risk profiles for the development of multiple sclerosis within 10 years after optic neuritis: experience of the optic neuritis treatment trial. Arch Ophthalmol. 2003;121:944–949.
4. Budenz DL, Chang RT, Huang X, Knighton RW, Tielsch JM. Reproducibility of retinal nerve fiber thickness measurements using the stratus OCT in normal and glaucomatous eyes. Invest Ophthalmol Vis Sci 2005; 46:2440–2443.
5. Kanamori A, Naka M, Nagai-Kusuhara A, Yamada Y, Nakamura M, Negi A. Regional relationship between retinal nerve fiber layer thickness and corresponding visual field sensitivity in glaucomatous eyes. Arch Ophthalmol 2008; 126:1500–1506.
6. Klistorner A, Arvind H, Nguyen T, Garrick R, Paine M, Graham S, et al. Multifocal VEP and OCT in optic neuritis: a topographical study of the structure-function relationship. Doc Ophthalmol. 2009a;118:129–137.

7. Warner CV, Syc SB, Stankiewicz AM, et al. The impact of utilizing different optical coherence tomography devices for clinical purposes and in multiple sclerosis trials. PLoS One. 2011;6: e22947.

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

9. Cettomai D, Pulicken M, Gordon Lipkin E, Salter A, Frohman TC, Conger A, Cutter G, Balcer LJ, Frohman EM, Calabresi PA. Arch Neurol. 2008;65(9):1218–1222.

10. 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.

11. Sutter EE. Imaging visual function with the multifocal m-sequence technique. Vision Res. 2001; 4: 1241–1255.

12. Hood DC, Greenstein VC, Odel JG, Zhang X, Ritch R, Liebmann JM, et al. The multifocal VEP and ganglion cell damage: applications and limitations for the study of glaucoma. Prog Retin Eye Res 2003;22:201-51.

13. Hood DC, Greenstein VC, Odel JG, Zhang X, Ritch R, Liebmann JM, et al. Visual field defects and multifocal visual evoked potentials: Evidence for a linear relationship. Arch Ophthalmol 2002;120:1672-81.

14. Dooley MC, Foroozan R. Optic neuritis. J Ophthalmic Vis Res. 2010;5(3):182–187.

15. Mamarabadi M, Razjouyan H, Mohammadi F, Moghaddasi M. Assessment of outcome predictors after first attack of optic neuritis. Can J Neurol Sci. 2011;38:887–895.

16. Lochner P, Leone MA, Coppo L, et al. B-mode transorbital ultrasononography for the diagnosis of acute optic neuritis. A systematic review. Clin Neurophysiol. 2016;127(1):803–809.

17. Bennett JL, de Seze J, Lana-Peixoto M, et al. Neuromyelitis optica and multiple sclerosis: seeing differences through optical coherence tomography. Mult Scler. 2015;21(6):678–688.

18. Optic Neuritis Study Group The 5-year risk of MS after optic neuritis: experience of the optic neuritis treatment trial. Neurology. 1997;49(5):1404–1413.

19. Gal RL, Vedula SS, Beck R. Corticosteroids for treating optic neuritis. Cochrane Database Syst Rev. 2012;8: CD001430.

20. Keegan M, Pineda AA, McClelland RL, Darby CH, Rodriguez M, Weinshenker BG. Plasma exchange for severe attacks of CNS demyelination: predictors of response. Neurology. 2002;58:143–146.

21. 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 Feb;20(2):183-91.

22. 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 Apr;16(4):412-26.

23. Beck RW. The Optic Neuritis Treatment Trial. Arch Ophthalmol. 1988;106:1051–1053.

24. Genova HM, Sumowski JF, Chiaravalloti N, Voelbel GT, Deluca J. Cognition in multiple sclerosis: a review of neuropsychological and fMRI research. Front Biosci. 2009;14:1730–1744.

25. 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;113:323.e1-323.e2.

26. Alshowaeir D, Yiannikas C, Garrick R, Parratt J, Barnett MH, Graham SL, et al. Latency of multifocal visual evoked potentials in nonoptic neuritis eyes of multiple sclerosis patients associated with optic radiation lesions. Invest Ophthalmol Vis Sci 2014;55:3758–64.

27. Jayaraman M, Gandhi RA, Ravi P, Sen P. Multifocal visual evoked potential in optic neuritis, ischemic optic neuropathy and compressive optic neuropathy. Indian J Ophthalmol 2014;62:299–304. http://dx.doi.org/10.4103/0301- 4738.118452.

28. Nebbioso M, Steigerwalt RD, Pecori-Giraldi J, Vingolo EM. Multifocal and patternreversal visual evoked potentials vs. automated perimetry frequency-doubling technology matrix in optic neuritis. Indian J Ophthalmol 2013;61:59–64.

29. Klistorner A, Graham SL. Objective perimetry in glaucoma. Ophthalmology 2000;107:2283–99.

30. Biogen Idec, 2014b. BIIB033 In Acute Optic Neuritis (AON) (RENEW). https://clinicaltrials.gov/ct2/show/NCT01721161 ?term=BIIB033 & rank=4 (retrieved 01.11.14).

31. Winn B, Shin E, Odel JG, Greenstein VC. DC Hodd. Interpreting the multifocal visual evoked potential: the effects of refractive errors, cataracts, and fixation errors. Br J Ophthalmol 2005;89:340–4.

32. Nakamura M, Kato K, Kamata S, Ishikawa K, Nagai T. Effect of refractive errors on multifocal

VEP responses and standard automated perimetry tests in a single population. Doc Ophthalmol 2014;128:179–89. http://dx.doi.org/10.1007/s10633-014-9431-4.

33. Hood DC, Greenstein V. Multifocal VEP and ganglion cell damage: applications and limitations for the study of glaucoma. Prog Retin Eye Res 2003;22:201–51.

34. Stensaas SS, Eddington DK, Dobelle WH. The topography and variability of the primary visual cortex in man. J Neurosurg 1974;40:747–55.

35. 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(1):41–8. http://dx.doi.org/10.1007/s10633-016-9546x. Epub 2016 Jun 16.

36. Frohman AR, Schnurman Z, Conger A, Conger D, Beh S, Greenberg B, et al. Multifocal visual evoked potentials are influenced by variable contrast stimulation in MS. Neurology 2012;79:797–801. http://dx.doi.org/10.1212/WNL.0b013e3182661edc.

37. Ruseckaite R, Maddess T, Danta G, Lueck CJ, James AC. Sparse multifocal stimuli for the detection of multiple sclerosis. Ann Neurol 2005;57:904–13.

38. De Santiago L, Fernandez A, Blanco R, Perez-Rico C, Miguel-Jiménez JM, Amo C, et al. Improved measurement of intersession latency in mfVEPs.Doc Ophthalmol 2014;129:65–9. http://dx.doi.org/10.1007/s10633-014-9438-x.

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