Clinical Neurophysiology 127 (2016) 1574–1580

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

A signal-to-noise-ratio-based analysis of multifocal visual-evoked potentials in multiple sclerosis risk assessment

L. De Santiago [a,b], M. Ortiz del Castillo [a,b], R. Blanco [c], R. Barea [a,b], J.M. Rodríguez-Ascariz [a,b], J.M. Miguel-Jiménez [a,b], E.M. Sánchez-Morla [d], L. Boquete [a,b,*]

[a] Biomedical Engineering Research Group, Department of Electronics, University of Alcalá, Plaza de S. Diego, s/n, 28801 Alcalá de Henares, Spain
[b] Department of Electronics, University of Alcalá, Plaza de S. Diego, s/n, 28801 Alcalá de Henares, Spain
[c] Department of Surgery and Medical Sciences, University of Alcalá, Plaza de S. Diego, s/n, 28801 Alcalá de Henares, Spain
[d] Department of Psychiatry, University Hospital of Guadalajara, Spain

ARTICLE INFO

Article history:
Accepted 18 September 2015
Available online 30 September 2015

Keywords:
Multifocal visual-evoked potentials
Signal-to-noise ratio
Optic nerve
Visual function
Multiple sclerosis
Expanded Disability Status Scale

HIGHLIGHTS

- Assessment of MS patients' visual function was improved by using signal-to-noise ratio (SNR) values at ring 5.
- Multifocal visual-evoked potentials' (mfVEPs) SNR values decreased as risk of developing MS increased.
- MfVEPs' ring 5 eccentricity amplitude was related to disability severity in MS patients.

ABSTRACT

Objective: To study the value of using the signal-to-noise ratio (SNR) of multifocal visual-evoked potentials (mfVEPs) in assessment of subjects at risk of developing multiple sclerosis (MS).
Methods: MfVEP signals were obtained from 15 patients with radiologically isolated syndrome (RIS), from 28 patients with clinically isolated syndrome (CIS), from 28 with clinically definite MS and from 24 control subjects. The CIS and MS groups were divided into two subgroups: those with eyes affected by optic neuritis (ON) and those without (non-ON). The mfVEPs' SNR was obtained for both the whole visual field and at various eccentric rings. The area under the curve (AUC) was calculated by comparing the control subjects' mfVEP SNR values with those of the RIS, CIS and MS groups.
Results: In whole visual field analysis, risk of developing MS increased as SNR decreased ($SNR_{CONTROL} = 0.70$, $SNR_{RIS} = 0.62$, $SNR_{CIS\text{-}nonON} = 0.54$, $SNR_{CIS\text{-}ON} = 0.40$, $SNR_{MS\text{-}nonON} = 0.52$, $SNR_{MS\text{-}ON} = 0.40$). Ring 5 (9.8°–15° eccentricity) was most affected by the SNR decrease, as indicated by its higher AUC values ($AUC_{FULL\_EYE} = 0.81$, $AUC_{RING\_5} = 0.89$). A significant relationship (Spearman correlation, $\rho_{RING\_5} = 0.61$) between SNR values and disability severity on the Expanded Disability Status Scale (EDSS) was observed in clinically definite MS patients.
Conclusion: A new method based on analysis of the SNR of mfVEP signal amplitude improves assessment of patients at risk of developing MS.
Significance: Improved mfVEP assessment of MS-risk patients was achieved by using SNR values at 9.8°–15° eccentricity of the visual field.

1. Introduction

Optic nerve and ganglion cell dysfunction can be studied in clinical settings using either conventional or multifocal visual evoked potential (VEP) techniques (Zhang et al., 2002). Baseler et al. (1994) and subsequent studies (Grippo et al., 2006; Klistorner et al., 1998; Yang et al., 2007) have shown that multifocal

* Corresponding author at: Department of Electronics, University of Alcalá, Plaza de S. Diego, s/n, 28801 Alcalá de Henares, Spain. Tel.: +34 91 8856572; fax: +34 91 8856591.
E-mail address: luciano.boquete@uah.es (L. Boquete).

http://dx.doi.org/10.1016/j.clinph.2015.09.129
1388-2457/

visual-evoked potentials (mfVEPs) can overcome most of the limitations of conventional VEPs, allowing simultaneous recording of local responses from many regions of the visual field. The mfVEP technique has been shown to be more sensitive than standard automated perimetry when used to detect early visual field defects in multiple sclerosis (MS) (Klistorner et al., 2008, 2012).

MfVEP signal amplitude or intensity is typically quantified as a signal-to-noise ratio (SNR) (Zhang et al., 2002). Several studies have demonstrated the applicability of analysing the SNR of mfVEPs in MS. Klistorner et al. (2008) and Laron et al. (2009) have shown, using whole visual field analysis, that the mfVEP signals' SNR decreases as MS progresses.

MfVEPs can reflect the state of the optic nerve by including information from fibres subserving more peripheral parts of the visual field. Taking simultaneous recordings from multiple visual field locations also produces high spatial resolution, allowing for independent assessment of multiple regions (Klistorner et al., 2008). To exploit this spatial information, Laron et al. (2009) calculated the SNR value per ring in MS patients and observed a reduction in SNR as eccentricity increased, showing that inner rings were more affected than outer rings (the rings are defined in Fig. 1).

In the present study, we aimed to examine the variation in mfVEP amplitude, quantified as SNR, across the visual field and looked at how the amplitude in each zone was related to the risk of developing MS. This variation was studied in a cohort of patients diagnosed as having either radiologically isolated syndrome (RIS), clinically isolated syndrome (CIS) or clinically definite MS. Over 80% of CIS patients who present lesions when assessed using magnetic resonance imaging (MRI) go on to develop MS, while approximately 20% follow a self-limited process. This may create a diagnostic and therapeutic dilemma given the difficulty of predicting which patients will develop clinically definite MS (Blanco et al., 2014; Frohman et al., 2003). RIS patients, on the other hand, are subjects whose MRI findings are typical of MS but who produce normal results on neurological examination (Moore and Okuda, 2009). As optic neuritis (ON) is an early clinical symptom in most cases of MS (Beck et al., 2003), subjects' eyes were classified as ON-affected or non-ON-affected.

Visual field zones' capacities were assessed to classify the eyes' mfVEP amplitudes as normal or abnormal based on a predefined detection threshold (abnormal means mfVEP amplitude values were atypical or anomalous when compared with control mfVEP amplitude values). This analysis was then compared with the cluster-based method, described by Hood and Greenstein (2003), used in most analyses of mfVEP recordings.

Abnormal mfVEP amplitudes were calculated according to visual field eccentricity and were compared with the patient's degree of disability, as quantified by the Kurtzke Expanded Disability Status Scale (EDSS) (Kurtzke, 1983).

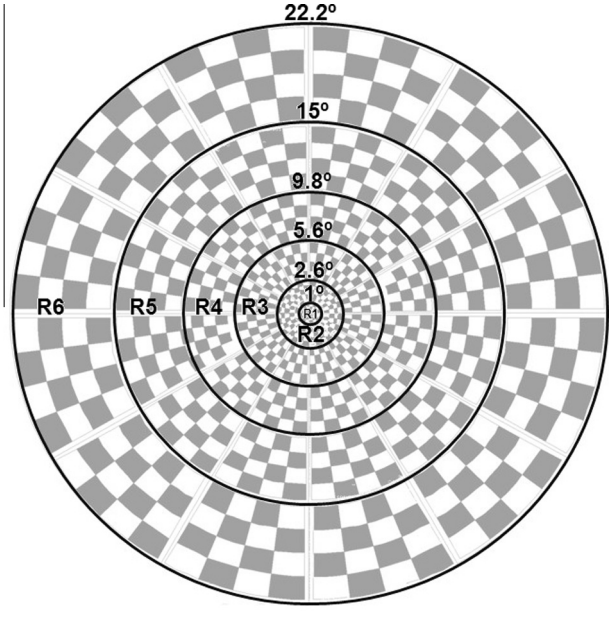

Fig. 1. Rings defined and degrees of each radius.

2. Patients and methods

The study protocol was approved by the Institutional Review Boards of University of Alcalá-affiliated hospitals and adhered to the tenets of the Declaration of Helsinki. All participants provided written informed consent.

A cohort of patients with clinically definite MS and at different relative risk of developing MS, classified as RIS and CIS (Table 1), was included in this study and compared with a control group. CIS and MS patients were divided into two subgroups — optic neuritis (ON) eyes and non-ON eyes — based on whether or not they had had prior clinical ON episodes. The notation is ON for eyes with a history of optic neuritis and non-ON for eyes without a history of optic neuritis. Examples of mfVEP recordings from each diagnosis group are shown in Fig. 2.

Inclusion criteria for RIS subjects (15 patients) were based on Moore and Okuda (2009) — MRI anomalies that did not account for clinically apparent impairments, and central nervous system (CNS) white-matter anomalies with the following criteria: (1) ovoid, well-circumscribed and homogeneous foci with or without involvement of the corpus callosum; (2) T2-hypertensities measuring >3 mm^2 and fulfilling 3 or 4 Barkhof Criteria for dissemination in space; and (3) CNS anomalies not consistent with a vascular pattern. Twenty-eight patients (CIS patients) having a first clinical episode suggestive of CNS demyelination involving the optic nerve, brainstem, spinal cord or other topography not attributable to other inflammatory diseases but lacking radiological evidence of dissemination of lesions over time were included in this study, as were 28 patients clinically diagnosed as suffering MS according to the McDonald criteria. Finally, 24 age-matched healthy subjects with normal neurological and ophthalmologic examination results were included as a control group.

2.1. MfVEP recordings

The method used to obtain the recordings is described in detail by Hood and Greenstein (2003) and Laron et al. (2009). MfVEP recordings were obtained using VERIS software 5.9 (Electro-Diagnostic Imaging, San Mateo, USA). The stimulus was a scaled dartboard with a 44.5° diameter containing 60 sectors with 16 alternating checks each — eight white (luminance: 200 cd/m^2) and eight black (luminance: <3 cd/m^2) — and a Michelson contrast

Table 1
Patient demographics.

	Control	RIS	CIS	MS
Number of subjects	24	15	28	28
Age (years)	30.30 ± 7.55	39 ± 7.8	30.29 ± 9.55	34.39 ± 10.09
Male:female ratio	10:14	5:10	10:18	7:21
EDSS	0	0	0.9 ± 0.8	1.26 ± 1.62
ON eyes	0 (0%)	0 (0%)	12 (21.4%)	37 (66%)
Non-ON eyes	48 (100%)	30 (100%)	44 (78.6%)	19 (34%)
Bilateral ON patients	0 (0%)	0 (0%)	2 (7.1%)	9 (32.2%)
Unilateral ON patients	0 (0%)	0 (0%)	8 (28.6%)	19 (67.8%)
Non-ON patients	24 (100%)	15 (100%)	18 (64.2%)	0 (0%)