New methods to detect multiple sclerosis

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Abstract. This paper describes multifocal visual evoked potentials (mfVEPs) recorded to different levels of temporal sparseness. It presents the usefulness and diagnostic value of mfVEPs in multiple sclerosis (MS) and optic neuritis (ON). The paper also discusses the usefulness of frequency doubling (FD) illusion and the effect of binocularity in Normal and MS study groups. © 2004 Elsevier B.V. All rights reserved.

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1. Introduction

Various types of visual evoked potentials (VEPs) have been used for the detection of MS [1]. MS is a central nervous system (CNS) disease, characterized by multiple areas of demyelination [2]. MS patients initially report abnormalities of vision, which are the result of lesions of the optic nerve causing ON. The studies [3] have also shown that VEPs obtained to both monocular and binocular stimuli were a useful tool in characterizing ON. Classification models based on a range of response measures were constructed to discriminate Normal subjects from those with ON in our study too. These models were then applied to MS patients who showed no previous ON. Sensitivities and specificities for both groups were estimated. We also investigated the effect of different chequerboard visual stimuli, FD illusion and binocularity.

2. Methods

2.1. Recording

MfVEPs were recorded in monocular, binocular and dichoptic viewing conditions to four levels of temporal sparseness: Binary, Sparse₄, Sparse₁₆ and Pattern Pulse. A more
detailed description of the stimuli can be found in the paper of Ruseckaite et al. [4] and James et al. [5]. FD illusion was tested using the FD technology (FDT) [6] and mfVEPs as described by Maddess et al. [7].

2.2. Subjects

For the first experiment, mfVEPs were recorded from 13 Normal subjects [5]. In the other experiments, responses were obtained from 50 MS patients and 27 Normal subjects [4]. The research followed the tenets of the Declaration of Helsinki, under the Australian National University’s Human Experimentation Ethics Committee under protocol M990.

3. Data analysis

We applied multiple regression method, described by James [8]. Within each response, we analysed two time periods, containing the first negativity N1 and the first positivity P1 [5]. To determine the peaks in MS patients, we examined the minimums and maximums of the running t-statistics [4]. The N1 and P1 implicit times were referred to as NT and PT.

To decompose the aberrant waveforms of the patients into a few delayed versions (NTF) of responses of Normal subjects, we developed TEMPLATE algorithm [4]. Linear and Quadratic Discrimination models [9] were applied to examine sensitivities and specificities of the responses.

4. Results

4.1. The effect of sparseness in Normal subjects

To know if there was an effect of temporal sparseness in Normal subjects, we compared the mfVEPs obtained with three levels of temporal sparseness: Binary, Sparse4 and Sparse16 [5]. Fig. 1 shows N1 means, averaged across all subjects, presented in an image format, where the stimulus regions are coloured according to the average N1 response for that region. The rows of panels in Fig. 1 represent the stimuli. The central two columns indicate

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Fig. 1. Monocular data versus dichoptic. The left columns represent voltage responses averaged across subjects for the eight regions of the left eye (OS), dichoptic (Di) and monocular (Mon) viewing condition.
average responses to monocular stimuli, and the outer two- to dichoptic viewing conditions. Light colours represent higher amplitudes, and darker regions—lower amplitudes for the N1 means, respectively. Notice that the rows have separate grey-level calibrations (vertical scale bars at right of each row). Here, the relatively greater suppression of responses to dichoptic Binary stimuli relative to dichoptic Sparse16 stimuli is very evident.

4.2. The effect of sparseness in MS patients

We were curious to examine the Sparser stimuli in MS patients, therefore here we introduced even sparser, Pattern Pulse stimulus [5]. The responses of MS patients were smaller compared with those obtained from Normal subjects (Sparse16*MS responses were smaller by 2.03±0.34 dB than the Binary responses of the Normal subjects (−9.97±0.71 dB)). The mfVEPs of MS patients were also significantly suppressed for the Pattern Pulse (−1.68±0.38 dB). NT were delayed in MS patients for all stimuli on average by 18.19±1.31 ms.

We examined Linear Discrimination models based on the response size, waveform shape and latencies, NT and NTF. High sensitivities and specificities of the model containing NTF medians and maximums were achieved for the Pattern Pulse stimulus (>95%). Both NT and NTF were able to discriminate more than 98% MS patients having no ON history [4].

4.3. FD illusion in MS patients

In our study, we also compared FDT thresholds and the FD mfVEPs obtained from Normal, MS and ON subjects. Fig. 2 illustrates the difference between FDT and mfVEPs in Normal subjects and patients. The FDT thresholds are clearly larger than the mfVEPs.

4.4. Binocular pattern pulse responses

We examined the binocular and monocular responses in Normal and MS patients and found that the responses in MS patients indicated a significant (p<0.05) decrease of N1 by

![Fig. 2. Multivariate regression coefficients and their S.E. for FDT and FD mfVEPs obtained from Normal (N), ON and MS patients. Note that the data are averaged across all subjects in each group.](image)
-1.45±0.48 dB compared with the responses of normal binocular vision (8.94 dB). To check if the binocular NT were predicted by one of the eyes, we fitted models containing the delays obtained from the best and the worst eye vs. the data from binocular viewing. Here the best eye had shorter implicit times compared with the other eye. In both Normal and MS study groups, the binocular delays were not influenced by either of the eyes particularly, but were intermediate.

5. Discussion

In agreement with previous studies [10,11], we found that the mfVEP waveforms of our patients were delayed, especially for Sparser visual stimuli. The best specificities and sensitivities of our discriminant models were obtained for the Pattern Pulse, the maximums of the fitted delays. The binocular N1 were larger than monocular N1 in both study groups, but smaller in ON patients. Their implicit times were almost the same in monocular and binocular cases, however, the responses were more delayed in MS and ON patients. FDT thresholds were smaller than FD mfVEPs in all study groups.

References