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Photopic and scotopic VEPs in patients with congenital stationary night-blindness

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Abstract

Extended set of visual evoked potentials (VEPs) using pattern-reversal (PREPs), linear motion-onset and radial (expansion) motion-onset stimuli (M-VEPs) (detailed specification at http://www.lfhk.cuni.cz/elf) was used to verify congenital stationary night-blindness (CSNB) characteristics in 7 patients (compared to 7 age matched controls) in photopic conditions (luminance of 17 cd/m^2). No differences were found in any of the M-VEPs, whilst PREPs displayed prolonged latencies in 3 of 7 CSNB patients. Additionally, the PREPs and M-VEPs were tested in 3 normal and 3 CSNB subjects (the only available ones from the original group) over large range of scotopic, mesopic and photopic luminances (from 0.0001 to 65.4 cd/m^2). Both types of low luminance VEPs had distinctly increased luminance threshold needed for reliable VEPs eliciting in CSNB patients (0.06 cd/m^2) when compared with controls (0.003 cd/m^2); the VEP appearance threshold was almost identical with the perceptual threshold in both groups. Thus, our pilot study proved that CSNB can be objectively detected also *via* scotopic VEP examination. Since the prolonged PREP latencies at 17 cd/m^2 normalised with luminance increase, it indicates that the lower luminance stimuli (compared to the standard recommended by ISCEV) can be more sensitive for some visual disorders detection.

Abbreviations: CSNB – congenital stationary night blindness; M-VEPs – motion-onset VEPs; PREPs – pattern-reversal VEPs.

Introduction

Congenital stationary night-blindness (CSNB) is a visual disorder characterised mainly by abnormal function of the rod system that results in worsened vision in dim light conditions. CSNB is at present almost exclusively diagnosed by means of ERG investigation that yields a very characteristic picture in these patients (e.g., [1, 2]). ERG also enables classifications of a particular case as one of the known subtypes (m. Schubert-Bornschein (complete or incomplete) and m. Riggs). No similar VEP characteristics have been described and the VEP testing is usually not performed in nyctalopic patients. In one of sporadic studies, Barnes and his colleagues [3] used successfully VEP testing for diagnose highlighting in a patient with a distinctive form of CSNB, the VEPs were, however, elicited by a quite unusual type of stimulus designed just for this purpose (incremental – decremental squares). In our study, we compared our standardly used VEPs (pattern reversal and motion onset ones) in nyctalopic and normal subjects to find out whether the VEPs can some-

how contribute to the visual function evaluation in CSNB patients. Moreover, we tried to develop a method for scotopic/mesopic VEP generation, because the attempts to record scotopic VEPs have been only rare so far. Benedek et al. recorded scotopic pattern-reversal VEPs [4]; later the same research group described also scotopic steady state VEPs [5]; these VEPs were, nevertheless, never tested in nyctalopic patients.

Methods

Stimuli (all available at http://www.lfhk.cuni.cz/elf/)

(1) *Photopic VEPs*. Transient pattern-reversal visual evoked potentials (P-VEPs) were acquired with high contrast (96%) square-wave black and white checkerboard (element size 20′, 40′ and 80′) reversing at the rate of 2 rev/s.
Two variants of motion-onset VEPs (M-VEPs) were used:

(a) *linear motion* (random order of fundamental directions, velocity 10 deg/s) of low contrast (10%) isolated checks (40′ check size and 120′ check-to check-distances).
(b) *centrifugal radial motion – 'expansion'* that consisted of low contrast (10%) grey concentric frames with increasing size (spatial frequency of 1–0.2 c/deg). These frames moved from the centre (fixation point) towards periphery at the velocity in range between 10 and 23 deg/s. Both the spatial frequency and velocity change towards periphery were set to respect the size of the retinal perception fields and sensitivity differences to motion velocity across the retina.

Both moving stimuli had the same timing – 200 ms of motion was followed by 1 s inter-stimulus interval (stationary pattern). In motion-onset VEPs, the latency and amplitude of the N160 peak was evaluated (this peak was shown to represent the main motion-onset related component of this VEP type – [6, 7]).

All visual stimuli were generated (using VSG 2.5 (CRS Ltd. UK)) on the 21″ monitor Iyama (Japan) with the vertical frequency of 100 Hz. The stimulus field subtended 45° × 35° in viewing distance of 0.5 m. The average luminance was 17 cd/m^2. Correct fixation of the centre of the stimulus field was monitored via infra-red CD camera.

(2) *Scotopic VEPs*. For scotopic VEPs eliciting the pattern-reversal and centrifugal radial motion of the same parameters were used. However, for pattern-reversal 5° check size was selected because of well known distinctly reduced visual acuity under the low luminance conditions.

Luminance

The CRT monitor luminance varied in a wide range of relative values 0–1000 representing zero to maximum input to digital/analog converter of the graphic card VSG 2/5 (CRS Ltd., UK). We used 15 relative levels (10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 150, 200, 300, 600 and 1000) corresponding to the range of luminances between 0.0001 and 65.5 cd/m^2 (set up by means of luminance regulation on the monitor).

The absolute luminance was measured directly with a photometer, for low luminances (bellow the photometer sensitivity) an indirect estimation method was used.

(a) *Direct measurement*. For direct measurement the OptiCAL photometer and LightScan software (CRS Ltd., UK) with photosensor 256 CRT (UDT Instruments USA) (accuracy ± 3%) were used. Obtained values are depicted in the Figure 1. The lowest reliable value was 0.35 cd/m^2 for the relative value 80.
(b) *Indirect methods*
    - *Extrapolation of the measured values* by a model of electro-optical transfer functions of our monitor – the classical gain-offset-gamma model. The results of the best-fitted exponential function are displayed in the Figure 1.
    - Method based on the *long exposition of digital camera* Photo Smart 912 (Hewlett Packard, USA). The camera took pictures for three exposing times (4, 1 and 1/30 s) in the low-end range of luminance. The pictures were digitally processed to get average relative values (conversion to grey scale selection of region of interest and averaging across the region). The relative camera values were transformed to the absolute luminance levels by linear trans-

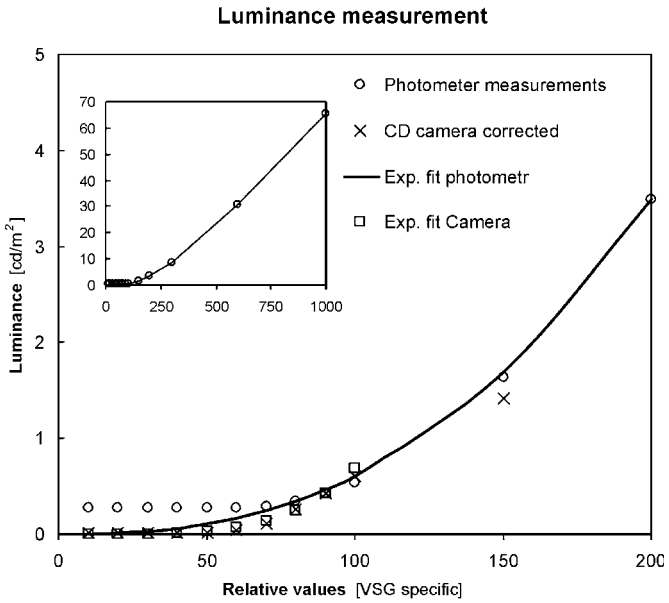

Figure 1. Graphic presentation of the results from low-level luminance measurements.

formation with coefficients obtained as the ratio of camera/measured values. This way we reached the value 0.02 cd/m^2 (relative value 50 on the input). To get values below this point we applied the same schema as in the first step.

Accuracy of the determined luminance values was verified by comparison of perceptual threshold in normal subjects with values reported in literature. Since the data acquired by the second method corresponded better to the literature data, these were considered for being more reliable and used (Figure 1).

Recording and data analysis

In the photopic part, monocular VEPs were recorded (our routine diagnostic practice). In the experimental scotopic part of the study we tested only binocular VEPs (because they are reported to have higher amplitudes than the monocular ones, which might be very important just at threshold luminance levels).

Standard recordings included pseudo-unipolar derivations (with the right ear lobe reference) from the midline Oz, Pz, Cz and Fz and also from Ol and Or (5 cm to the left and right from the Oz position). These lateral recording sites were used, since N170 motion-onset specific peak is mostly lateralised (irrespective to a dominant hemisphere) toward the temporo-occipital cortex [6]. For further evaluation, the data from the derivation with maximum response (typically Oz in pattern-reversal VEPs and Ol, Or or P_Z in motion-onset VEP) were taken.

Forty single VEPs (440 ms epochs with sampling frequency 500 Hz) were averaged. To verify a possible contamination of motion related VEPs by eye movements, in three subjects both horizontal and vertical electro-oculograms were also recorded (electrode placement on outer canthi and above and below the right eye). No significant eye movement related activity was found.

Subjects

The examinations of patients and control subjects were agreed in advance by the Ethical Committee of our Faculty of Medicine and they were done with the full consent of the subjects.

The study started with standard (photopic) examination of seven patients with CSNB upon the request of ophthalmologists. Only later we prepared experimental conditions for mesopic and scotopic VEP testing. Unfortunately, only three out of seven patients were available and agreed to participate in the extended voluntary experiments.

(1) *Photopic VEP comparison*. Seven patients with CSNB (five with complete CSNB, two with incomplete CSNB, mean age of 17) were examined; all diagnosed by ERG in Ophthalmologic department of the Faculty hospital; their myopia (hypermetropia in one case) and ev. astigmatism were always corrected as much as possible (visual acuity was 4/4 or 4/8 in most cases; in one subject it was, however, 4/32 and 4/20).

Seven age matched subjects with normal vision served as a control group.

(2) *Scotopic and mesopic VEP comparison*. For the scotopic and mesopic part of experiments, only three patients (all with diagnose of complete CSNB and with corrected myopia) were available and accordingly three controls with distinct VEPs to photopic condition stimuli were selected from the 'photopic' experimental group.

'Scotopic' experiment design

The subjects were adapted to dark for 30 min (they sat in completely light shielded experimental space) and than the stimuli were presented in sequence from the lowest luminance to higher ones. In the range of very low luminance levels, the subjects were asked prior to and after each stimulus presentation, whether they have seen anything or not and in this way the psychophysical threshold was obtained. The pattern-reversal and motion-onset VEPs were recorded in two separate sessions. The VEPs to each condition were recorded twice and the average of the two values was taken as the result.

Results

In our standard examination conditions (using low luminance of 17 cd/m^2), we have found in three patients (out of seven) that the reversal P1 latencies exceeded the upper limits of norm (for 20′, 40′ and 80′ check sizes they represent in our lab 124.6, 123.8 and 128.3 ms, respectively). However, the amplitudes of the PREPs as well as amplitudes and latencies of the VEPs to linear and radial motion stimuli were fully comparable in nyctalopic and normal group.

In scotopic and mesopic conditions all three examined normal subjects reported first visibility of the reversal stimuli (a shift of 'something' at the moment of pattern reversal only) at the luminance level of 0.003 cd/m^2 and at this luminance, also clear responses to pattern-reversal stimulus appeared. In three nyctalopic patients, who reported visibility threshold at the 10 times higher luminance (0.03 cd/m^2), the first reliable pattern-reversal responses came up only at luminance of 0.06 cd/m^2 (subject P1 in Figure 2) or even at 0.1 cd/m^2 in two subjects (P2 and P3), which clearly falls to 'mesopic' range [8]. With increasing luminance the latency of the main

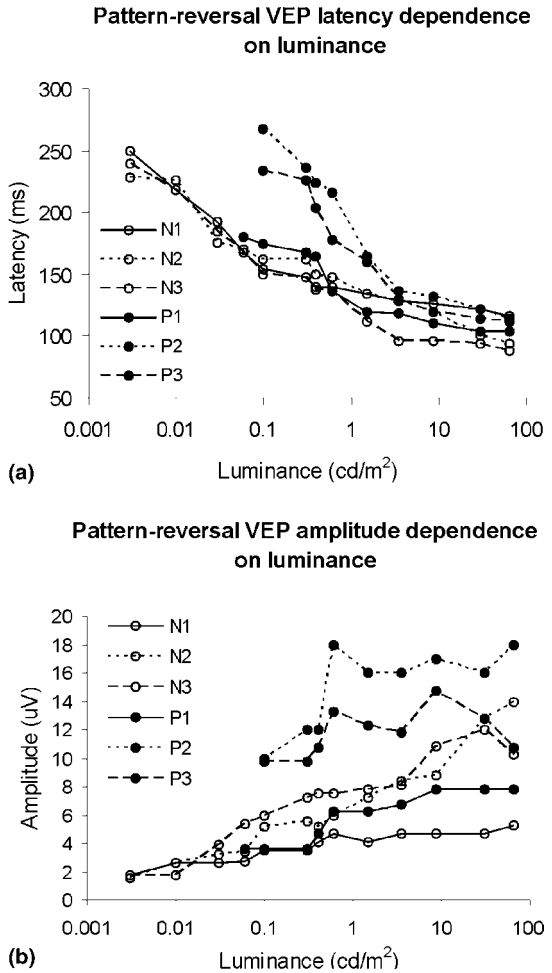

Figure 2. Latencies and amplitudes of pattern-reversal VEPs in normal subjects (N1–N3) and in patients with CSNB (P1–P3) over the tested range of luminance. Patients P2 and P3 with significantly prolonged latencies of VEPs up to luminance of 30.5 cd/m^2 were children 8 and 12 years old. These two patients also displayed abnormal pattern-reversal latencies in 'photopic' experiment (luminance of 17 cd/m^2).

positive peak of pattern-reversal VEP decreased and its amplitude increased (Figure 2).

In two of the three normal subjects, the low luminance reversal VEPs resembled rather the motion-onset VEP having prominent negative peak (left part of Figure 3). For that reason we additionally tested also the VEPs to radial motion onset over the whole range of luminance; this was performed in one normal and two nyctalopic subjects. The resulting VEPs are presented in the right part of Figure 3. It is evident that motion stimulation yields substantially larger responses in both the normal and nyctalopic subject, especially at low luminance levels. Again, the manifestation of distinct response corresponded exactly with the psychophysically revealed visibility threshold in the normal subject (luminance level of 0.003 cd/m^2). In the patients with CSNB, the stimuli were seen one or two steps earlier than the response came up (at luminance of 0.06 cd/m^2 in one subject and 0.1 cd/m^2 in the other subject). Figure 4 shows that with luminance increase the N160 latencies shortened and amplitudes increased.

Discussion

We did not find any difference between the group of normal subjects and patients with CSNB upon photopic conditions in the VEPs to motion stimuli. This is consistent with study of Wolf and Arden [9], who psychophysically compared parvo- and magnocellular pathway functions in patients with CSNB and with melanoma-associated retinopathy (MAR). They concluded that in contrast to MAR patients showing a selective magnocellular function deficit, the CSNB patients displayed relatively normal both parvo- and magnocellular functions. Rather unexpectedly, we have, however, found that the pattern reversal VEP latency was abnormal in three out of seven nyctalopic patients. All these three patients had complete form of CSNB; their visual acuity was quite successfully corrected and ophthalmologic testing did not reveal any other problem which could explain the prolonged P1 latencies. Although to our knowledge such a finding has not been reported so far, we believe that this is somehow connected to diagnosis of CSNB. The delayed response was, nevertheless, present only at luminance lower than about 30 cd/m^2, at higher luminance the latencies became completely normal. Most laboratories use relatively high luminance stimuli (ISCEV VEP standard [10] recommends luminance of about 46 cd/m^2), whilst in our laboratory traditionally 17 cd/m^2 is applied – this tradition was based on those studies that reported increased rate of multiple sclerosis detection along to lumi-

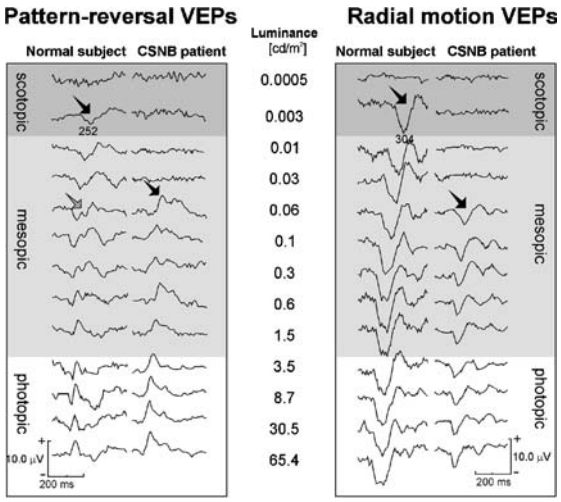

Figure 3. Particular pattern-reversal and radial motion-onset VEPs over whole range of the used luminance in a normal subject and in one patient with complete CSNB. Black arrows point to appearance of reliable peaks in responses. In the pattern-reversal VEP from the normal subject the response consists of negative peak only in scotopic conditions, later (mesopic conditions) the P1 peak appears as well (grey arrow).

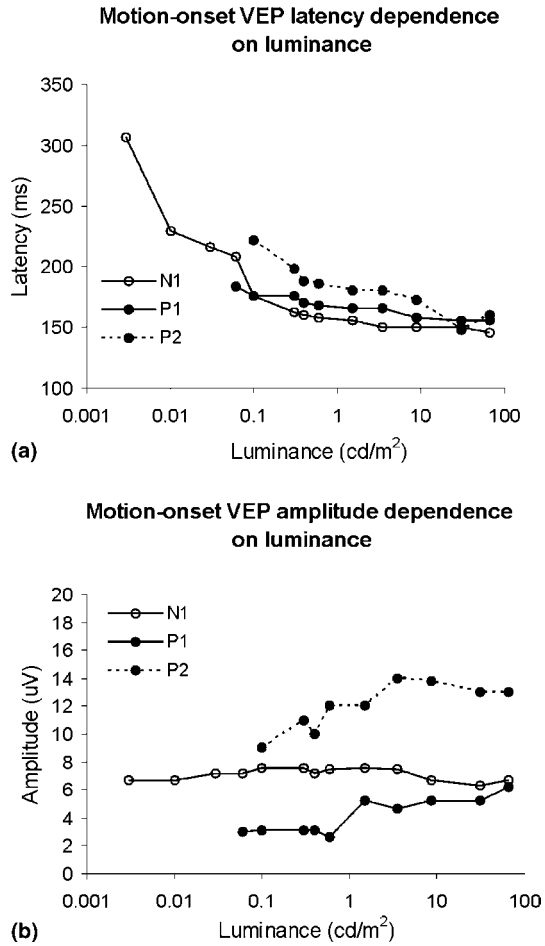

Figure 4. Latencies and amplitudes of motion-onset VEPs in one normal subject (N1) and two nyctalops (P1, P2). N1, P1 and P2 are the same subjects as N1, P1 and P2 in Figure 2.

nance decrease [11, 12]. These findings were later contradicted by Diener and co-workers [13] for multiple sclerosis diagnosis. Our study, however, seems to support the use of lower luminance stimuli for detection of at least some visual pathway disorders – we intend to test this idea in our future research.

The main finding of our study is that the VEPs – both to reversal and motion stimuli are obtainable at very low luminance levels. In normal subjects the first reliable responses popped out already at the luminance level of 0.003 cd/m^2; at this luminance also the perceptual threshold was reported. We did not measure the pupil diameter, but if the average pupil size 6.2 ± 0.9 mm reported for scotopic condition [e.g., 14] is taken, the resulting retinal illumination for luminance of 0.003 cd/m^2 is in the range between 0.047 and 0.13 trolands. Similarly to findings of Benedek and his co-workers [5] who described scotopic pattern-reversal VEPs (to lowest luminance of 0.004 cd/m^2, however, with pupil diameter fixed to 3 mm by use of an artificial pupil positioned in front of the eye) in normal subjects, 'our' scotopic PREPs consisted of a negative peak mainly/only and so its shape resembled rather a motion-onset VEP, especially in derivations from parieto-temporal cortex. Since the subjects reported 'seeing no pattern, but a movement', we suppose that pattern reversal stimulus activates mainly the magnocellular system under scotopic conditions. This is not surprising then that the motion-onset VEPs were easily obtainable as well and that they had even larger amplitudes than the reversal ones (see Figure 3). The predominance of 'motion-related' response is quite consistent with the generally known fact that upon scotopic conditions the vision is ensured only by rods that have dominant input to the magnocellular pathway (e.g., [15, 16]) – the eventual weaker rod input into parvocellular pathway is in detail discussed by Gegenfurtner and his colegues [17]. This all suggests that for VEP testing at very low luminance levels, a well arranged motion stimulus (e.g., radial motion) is recommendable.

In comparison with normal subjects, the patients with CSNB displayed significantly increased luminance threshold needed for eliciting of reliable VEPs – both pattern-reversal and motion-onset VEPs came up as late as at luminance of 0.06 cd/m^2 or even of 0.1 cd/m^2. The absence of 'scotopic' and low luminance 'mesopic' VEPs can be thus taken as an additional objective method for CSNB diagnosis. The luminance at which the responses appear shows also objectively the visual conditions at which the nyctalopic patients are able to orient themselves in a gloom environment.

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