

Steady-state multifocal visual evoked potential (ssmfVEP) using dartboard stimulation as a possible tool for objective visual field assessment

Folkert K. Horn¹ · Franziska Selle¹ · Bettina Hohberger¹ · Jan Kremers¹

Received: 12 August 2015 / Revised: 14 October 2015 / Accepted: 27 October 2015 / Published online: 9 November 2015
© Springer-Verlag Berlin Heidelberg 2015

Abstract

Purpose To investigate whether a conventional, monitor-based multifocal visual evoked potential (mfVEP) system can be used to record steady-state mfVEP (ssmfVEP) in healthy subjects and to study the effects of temporal frequency, electrode configuration and alpha waves.

Methods Multifocal pattern reversal VEP measurements were performed at 58 dartboard fields using VEP recording equipment. The responses were measured using m-sequences with four pattern reversals per m-step. Temporal frequencies were varied between 6 and 15 Hz. Recordings were obtained from nine normal subjects with a cross-shaped, four-electrode device (two additional channels were derived). Spectral analyses were performed on the responses at all locations. The signal to noise ratio (SNR) was computed for each response using the signal amplitude at the reversal frequency and the noise at the neighbouring frequencies.

Results Most responses in the ssmfVEP were significantly above noise. The SNR was largest for an 8.6-Hz reversal frequency. The individual alpha electroencephalogram (EEG) did not strongly influence the results. The percentage of the records in which each of the 6 channels had the largest SNR was between 10.0 and 25.2 %.

Conclusion Our results in normal subjects indicate that reliable mfVEP responses can be achieved by steady-state stimulation using a conventional dartboard stimulator and multichannel electrode device. The ssmfVEP may be useful for

objective visual field assessment as spectrum analysis can be used for automated evaluation of responses. The optimal reversal frequency is 8.6 Hz. Alpha waves have only a minor influence on the analysis. Future studies must include comparisons with conventional mfVEP and psychophysical visual field tests.

Keywords Steady-state · Multifocal VEP · Pattern reversal · Objective visual field test · Signal-to-noise ratio

Introduction

Multifocal visual evoked potentials (mfVEPs) can be used to assess the visual function of the central visual field [1]. The method may be an objective electrophysiological tool for detection of visual field losses [2–7]. Recent studies have revealed the presence of topographical associations between losses in mfVEP and structural damages in patients with optic nerve disorders [4, 8, 9, 10]. In mfVEPs, the electrical responses elicited by locally presented pattern reversals are recorded. Figure 1a shows an example of a conventional mfVEP in a normal subject as measured with commercial equipment. Pattern reversal dartboard stimuli for evaluation of transient signals were presented monocularly on a thin-film transistor (TFT) flat screen. The mfVEP can be recorded from the skull by placing a number of electrodes at different positions [11, 12]. Different configurations have been suggested to optimize amplitudes for the position and number of the electrodes as measurements at the brain are considerably influenced by anatomical features of the brain and their inter-individual variability [12, 13]. To reduce the influence of the cortical shape on waveform and magnitude of the signals, multichannel recordings for mfVEP measurements are recommended [12]. The best of the recorded signals from these channels, e.g.,

✉ Folkert K. Horn
folkert.horn@uk-erlangen.de

¹ Department of Ophthalmology and University Eye Hospital, Friedrich-Alexander University Erlangen-Nürnberg, Schwabachanlage 6, 91054 Erlangen, Germany

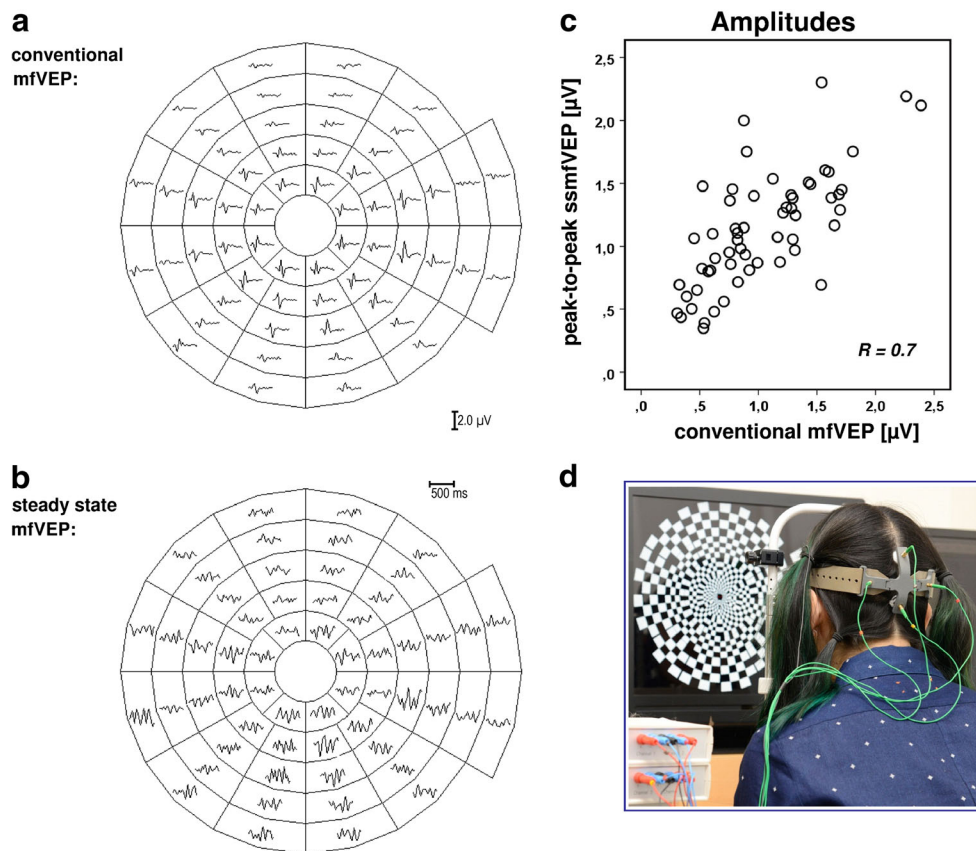


Fig. 1 Conventional mfVEP (**a**) and a steady-state mfVEP (**b**) from the same left eye of one participant (female subject: CR) measured with the RETIscan system (Roland Consult, Germany). The ssmfVEP was measured 24 days after the conventional mfVEP (both: 9.00 a.m.). Both methods used the same spatial configuration (dartboard stimulus), position of the electrodes, and number of averaged cycles. (**c**) Scatter plot of peak-to-peak amplitudes (i.e., twice the fundamental component) of ssmfVEP vs. peak-to-trough amplitudes of conventional

mfVEP. Amplitudes from steady-state stimulation were defined as the amplitude at the reversal frequency after spectral analysis of the signal (7.5 Hz). Peak-to-trough amplitudes in the conventional mfVEP were automatically determined by the commercial software ('RETIscan', LT4 protocol: 'best of' mode). The correlation coefficient between amplitudes from both methods was highly significant (Spearman: $p < 0.001$). (**d**) Measurement setting with a TFT stimulator and four-channel mounting device

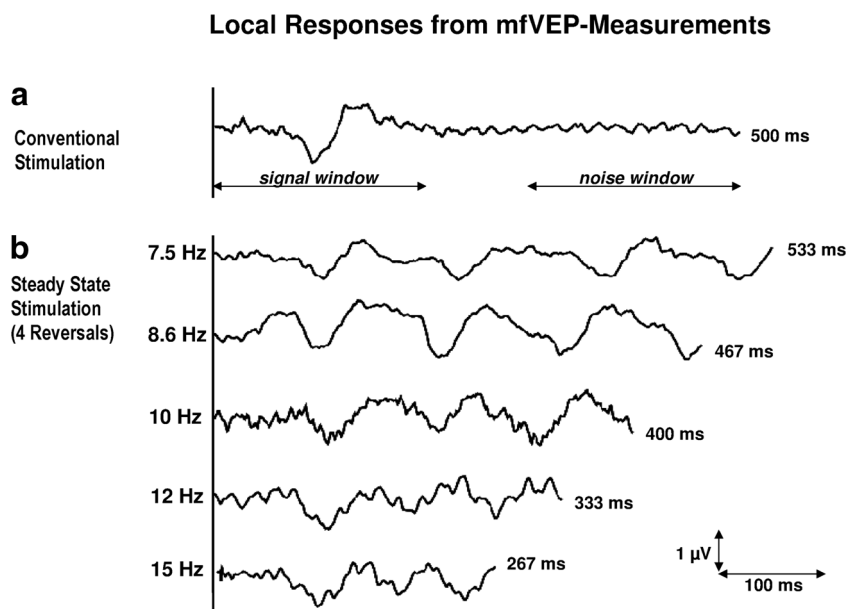
defined by the largest signal-to-noise ratios (SNR), can then be automatically selected by the analysis software. The SNR in the conventional mfVEP considers the signal amplitude in a predefined time window after pattern reversal in which the VEP response is expected to appear in relation to a part of the recording in which no response is elicited and the recording, thus, is solely determined by noise. The SNR data can be used not only for selection of the optimal electrode channel but also as a measure of the response quality and for correlation analysis with results from other ophthalmological procedures (e.g., perimetry) [8, 14, 15]. Figure 2a (topmost trace) shows an example of a single mfVEP response as obtained at a single location. The analysis time in this example (retiscan, LT4 protocol) was 500 ms, allowing the identification of a response (between 0 and 200 ms) and a noise period (between 300 and 500 ms after pattern reversal) [14, 16].

Thus, in conventional setups the quantification of the SNR uses the voltage levels in different time windows in the presence or absence of a signal. An alternative procedure to

separate signal and noise is offered by spectral analysis of steady-state signals with reversal rates that are so high that most energy of the response is concentrated at the reversal frequency. After Fourier transform of the recordings, the SNR values at all measured channels can be computed by using the signal amplitude at the reversal frequency and the noise defined as the averaged amplitudes at the neighbouring frequencies where no response is elicited.

The interest in steady-state multifocal VEPs (ssmfVEPs) [17–20] has been recently raised with the growing interest in 'brain-computer interface' (BCI) systems, where brain-controlled machine activities are under visual control because the gaze direction can be determined based on VEP responses. For example, a wheelchair could be controlled by gazing at different patches with pattern reversals at different frequencies [21] (e.g., 13 Hz=driving left, 14 Hz=driving right, etc.). In contrast to the multi-frequency [22] technique in which appropriate devices are needed to present different frequencies at different locations, the stimulus frequency in the mfVEP is the

Fig. 2 Examples of local responses in the conventional mfVEP (**a**) and in steady-state mfVEP (**b**) measured in the same eye at different sessions (stimulus location: nasal inferior, innermost ring). The steady-state measurements always used four pattern reversals



same at all test locations and m-sequence technique is used. For an optimal use of the ssmfVEP as a brain–computer interface it is crucial that the conditions resulting in VEPs with maximal SNRs are known.

It is, however, not known if a conventional monitored-based setup can be used to measure ssmfVEPs. There are neither general guidelines for the optimal temporal frequency and electrode configuration. A possible further problem with steady-state measurements is that alpha waves of the electroencephalogram (EEG) can contain large components at the reversal frequencies (between 5 and 15 Hz) for VEP measurements, thereby possibly interfering with the VEP signal [23]. The purpose of the present study was, therefore, to investigate whether a conventional monitor-based mfVEP system with an m-sequence technique can be used to record ssmfVEP in healthy subjects. Steady-state responses to different reversal frequencies were measured and the optimal temporal frequency, defined as the frequency with the largest SNR, was determined. Furthermore, the effects of electrode configuration and alpha EEG were studied.

Methods

Steady-state mfVEP recordings

Stimulus

A standard pattern-reversal dartboard stimulus with 58 fields was presented monocularly on a 19-inch TFT flat screen ('RETIsystem', Roland Consult, Brandenburg). The dartboard stimulus (radius: 30°) had 5 rings with 12 pattern reversal fields (8 black and 8 white check elements

each) and two nasal wings (43°). The angles between fixation and centre of the stimulus fields were: 2.3° , 5.3° , 10.2° , 16.7° , 24.7° , and 36.6° . The stimulus monitor ('ProLite X 486S', Iiyama, Japan) revealed a short reaction time (2 ms), a high ratio between maximal and minimal luminance (700:1) at nominal 100 % contrast and a high mean luminance (361 cd/m^2) that was used during the experiments. The maximal spatial deviation from the mean luminance was 16 % in the area of the dartboard stimulus. A detailed description of the present monitor and a comparison with a conventional monitor has been given earlier [24]. The optimally refracted subjects were instructed to fixate on a 'running' text (150 words) in the middle of the stimulus area (distance: 25 cm). The measurements were made with natural pupils.

A monitor with a 60-Hz frame rate was used and, therefore, temporal stimulation at multiples of the frame frequency was possible. Table 1 presents all pattern reversal characteristics that were studied in the present investigation. All ssmfVEP recordings were made with m-sequence multifocal stimulation with four reversals per m-step in every stimulated area. Thus, the length of a single m-response (Fig. 2b) varied between 266.6 and 666.6 ms. The time to perform one cycle, containing 256 m-steps, was between 68.3 s (at 15 Hz) and 170.7 s (at 6 Hz). Each measurement included 8 continued cycles (separated by an approximately 20-s rest period). The 6-Hz measurements were performed in 3 subjects only. The other subjects skipped 6-Hz testing because the recording time was too long, increasing the risk of fatigue. To avoid fatigue of the subjects, maximally two mfVEP measurements were completed per session. Only one session was performed per day.

Table 1 Present stimulus parameters are determined by the frame rate of the monitor system (multiple of 16.6 ms)

Frequency [Hz]	Frequency resolution [Hz]	Number of frames	Time of local recording m-step length [ms]	Time of one cycle [s]
6	1.5	4 * 10	666.7	170.7
7.5	1.9	4 * 8	533.3	136.5
8.6	2.1	4 * 7	466.7	119.5
10	2.5	4 * 6	400.0	102.4
12	3	4 * 5	333.3	85.3
15	3.8	4 * 4	266.7	68.3

VEP recording

VEPs were recorded using four different electrodes placed on the subject's skull using a cross-shaped electrode fixation device (positioned relative to theinion: 3.5 cm above, 3 cm below, and 4 cm to the left and right) [6]. Signals from four electrode pairs were differentially amplified. Biosignals were digitized with a 1-kHz sampling frequency and band pass filtered with 1- and 100-Hz cut-off frequencies. Figure 1b shows an example of an ssmfVEP measurement with this technique. Recordings from the 58 locations and 4 electrical channels were separately exported. The differential recordings from two additional electrode pairs [12] with different orientations were derived from the measured signals (Fig. 3a). The signals were subsequently analyzed with custom-written software. The analysis included a spectral analysis of the signals and a measurement of the response amplitude (F) at the reversal frequency and of the SNR in each of the six channels. SNR was computed by dividing the response amplitude by the

noise that was defined as the averaged amplitudes at the right and left neighbouring frequencies (Fig. 3b, first noise amplitude left side from $F=NL1$) [25]. It is assumed that no response is elicited by the stimulus at these adjacent frequencies in the spectrum. In addition to this conventional estimation of SNR using two flanking frequencies, we calculated the SNR by using four neighbouring frequencies for the determination of noise [i.e., $SNR_4 = F / \text{mean}(NL1, NL2, NR1, NR2)$]. Furthermore, we studied the influence of the alpha activity [i.e., the amplitude at an individual alpha frequency (IAF)] on the SNR. In that case, the SNR with four adjacent frequencies was performed with exclusion of the frequency that was nearest to the IAF (i.e., SNR calculations used three noise frequencies in most of the cases and used four noise frequencies when an IAF was close to the reversal frequency). The best SNR from the six electrode channels was selected. Finally the range of statistical noise was estimated for stimulated areas. This calculation used the 8.6-Hz measurements from nine subjects. However, instead of using the amplitude at the reversal

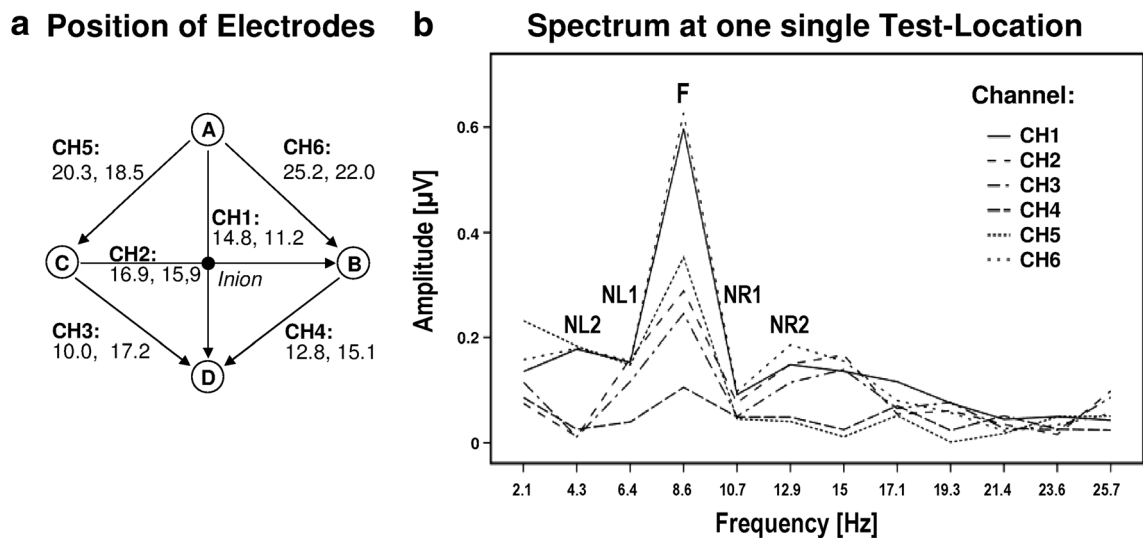
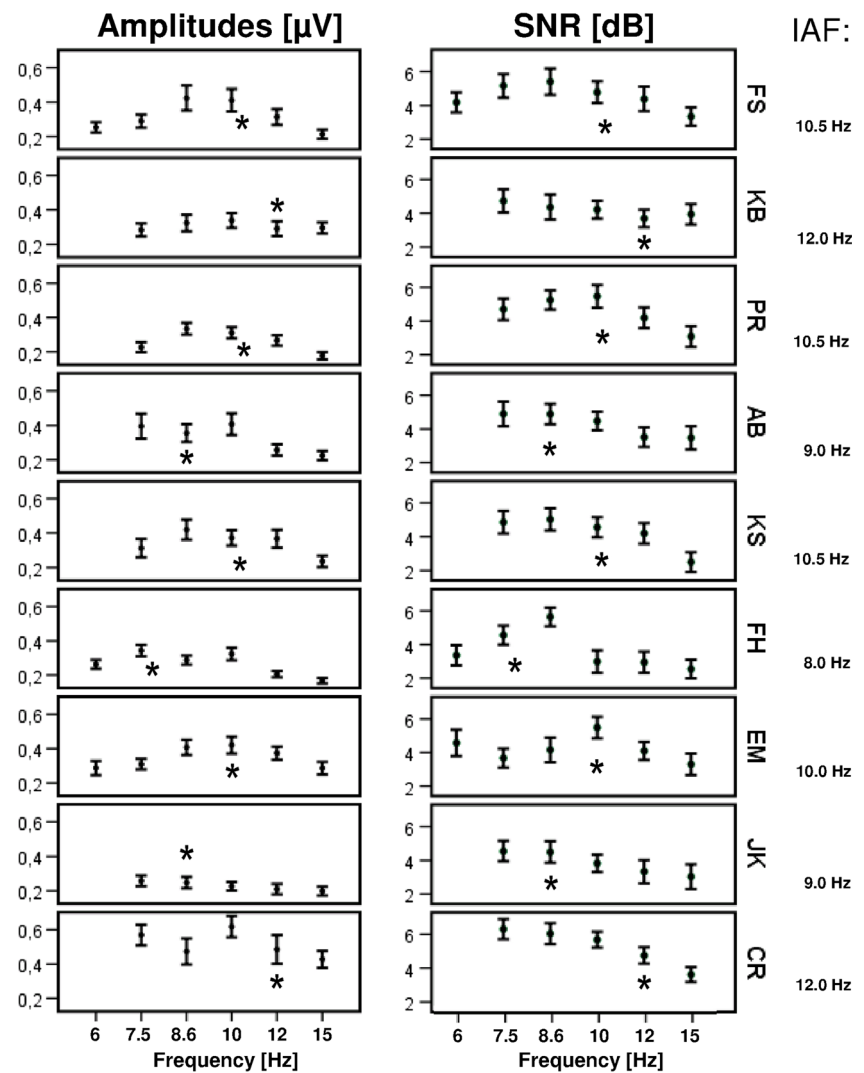


Fig. 3 (a) Sketch of electrode positions. Biosignals were recorded with four electrodes over the primary visual cortex (V1). Four measured channels (CH1–CH4) and two derived channels (CH5, CH6) were used for spectrum analysis. The percentage of the records in which each channel had the largest SNR was calculated using the 8.6-Hz

measurements from nine subjects (percentages [%] for left, right eyes). (b) The Fourier spectrum of all channels at a single test location. At this test location, the reversal amplitude was largest at channels 1 and 6. F : amplitude at reversal frequency; NL , NR : amplitudes at left and right flanking noise frequencies, respectively

Fig. 4 Mean reversal amplitudes (left column) and SNRs (right column) of ssmfVEPs for all subjects as a function of the stimulus reversal frequency. Mean values and error bars (95 % CIs) represent all focal responses (58) from each measurement. The measurements at the 6-Hz reversal frequency were performed in three subjects only. The IAF is indicated by asterisks



frequency, the amplitude at the right or left adjacent non-stimulus frequency (e.g., NR1) was divided by the mean of two other neighbouring non-stimulus amplitudes [in this case: $\text{NR1}/\text{mean}(\text{NL1}, \text{NR2})$]. Observe that this results in a noise-noise-ratio (NNR) which can be expected to be 1 on average. For comparison with the SNR, the same ‘best of six’ method was used for NNR calculation. Due to this procedure, the NNRs will be larger than 1.

Subjects and procedures

VEP measurements were performed on 9 randomly selected eyes of 9 healthy subjects (6 females, 3 males, mean age: 39.6 ± 16.4 years, range: 23–59 years). Slit lamp inspection, white-on-white perimetry with ‘Octopus’ (program G1), tonometry, and funduscopy were normal and the subjects were without medication. All individuals had clear optic media, a refractive error between -6 and $+4$ dB, and a visual acuity of 6/7.5 or better. All subjects were experienced in sensory tests. The IAF

was determined in all subjects by EEG measurements (frequency resolution: 1.5 Hz) with closed eyes using the same electrodes as in ssmfVEP. The IAF was the frequency component with the highest amplitude of the Fourier spectra of these measurements. The measurement of the IAF was repeated at least once. The study followed the tenets of the Declaration of Helsinki for research involving human subjects. The study has been registered at www.clinicaltrials.gov (NCT00494923) and was approved by the local ethics committee. Informed consent, including agreement for data collection, was obtained from all participants.

Statistical methods

The graphical presentations of the results display means and 95 % confidence intervals (CIs). Higher harmonic components and phase values were not considered. SNR data were evaluated after logarithmic transformation that was needed to achieve a normal distribution [13]. All

analyses were performed by SPSS 19 (SPSS-Inc., Chicago, USA). The level of statistical significance was $\alpha=0.05$. The power calculation indicates that our study with 9 subjects is able to reveal significant results with a probability of 90 %. Correlations between transient and steady-state VEP used Spearman's rank correlation.

Results

An example of an ssmfVEP measurement in comparison to a conventional mfVEP recording (RETIscan, LT4 mode) from the same eye is shown in Fig. 1. Measurements were made on different days in the left eye of a 55-year-old female observer. In this subject, pair-wise comparison revealed a strong correlation between the amplitudes of the steady-state and the conventional mfVEPs (Fig. 1c; fundamental component in the ssmfVEP; peak-to-through amplitude of the conventional mfVEP; Spearman's correlation coefficient $R: 0.7$, $p<0.001$).

The SNR in the ssmfVEP was calculated with the components in the frequency domain after spectral analysis (see Fig. 3b and Methods). As we wanted to determine which electrode pair was optimal, we calculated the

relative occurrence of the largest SNR for each channel (see Figs. 1d and 3a). The calculations were made for measurements from right (four subjects) and left (five subjects) eyes using the 8.6-Hz responses. The percentage of the records in which each of the 6 channels had the largest SNR was between 10 and 25.2 %.

Figure 4 presents the mean SNRs (using the directly adjacent frequencies and without exclusion of alpha frequencies) and the mean amplitudes of all 58 local responses plotted separately for each subject. In addition, Fig. 4 displays the individual IAFs which varied between 8 and 12 Hz (*asterisks*). For one subject (EM) the frequency for a maximal ssmfVEP amplitude and a maximal SNR coincided with the IAF, whereas they differed for the other subjects.

The SNR is a more useful quantification of the quality of the signal than response amplitude without consideration of the noise. For SNR calculation, the amplitude at the reversal frequency that is composed of noise plus the 'true' signal response is divided by a 'pure noise' estimate. Previously, one or more amplitudes at non-stimulus frequencies were used for pure noise estimates [25, 26]. In this study, three different noise estimates were compared (see also Methods section): noise was calculated from two neighbouring frequencies (1); from four neighbouring frequencies (2); and from four neighbouring frequencies with exclusion of the frequency closest to the IAF (3). Figure 5 shows the results of mean SNR calculations from all subjects as a function of pattern reversal frequency with these methods. All three SNR calculations showed a maximum at a reversal frequency of 8.6 Hz. The presentation suggests that the most commonly used method to calculate the SNR (using two nearest flanking frequencies for the calculation of noise) is superior to methods with more neighbouring frequencies. Based on these results, subsequent SNR analyses used the two adjacent frequencies for the calculation of noise.

Finally, the SNR values were determined for areas grouped as suggested earlier [12] (Fig. 6). To judge the value of these calculations, we calculated NNRs (see methods section). As expected we obtained mean noise ratios from non-stimulus frequencies that were very close to unity for all single channels. In the presentation of signal and noise we always selected the largest SNR value from the six channels. With this method, the range of the NNR in Fig. 6 was between 0.6 and 3.2 dB. The SNR showed a systematic dependence on stimulus location at all frequencies. Comparing SNRs at each frequency with NNRs we found significant differences for the 7.5-, 8.6-, and 10-Hz measurements. For the 12- and 15-Hz measurements, however, the responses in the far periphery were indistinguishable from noise.

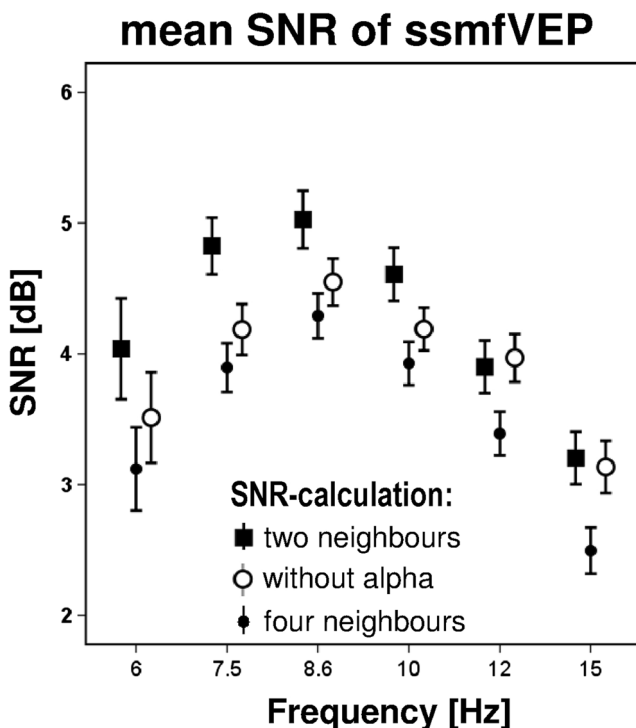


Fig. 5 Mean SNR ($\pm 95\%$ CIs) at different stimulus frequencies calculated using three different analysis methods: 1: using two neighbouring frequencies (NL1 and NR1 in Fig. 3; squares). 2: using four neighbouring frequencies (NL1, NR1, NL2 and NR2, filled circles). 3: as in 2 with exclusion of the component closest to the IAF (open circles)

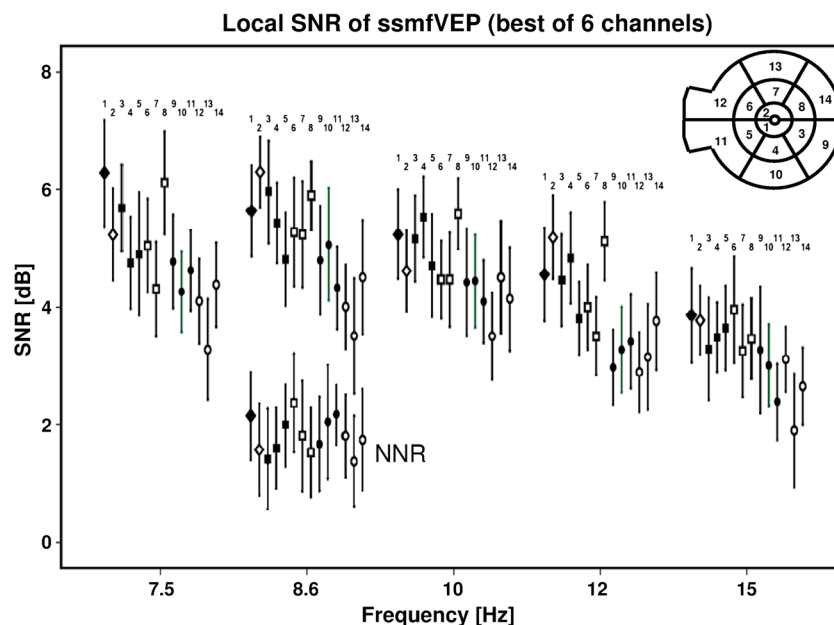


Fig. 6 Mean SNR from ssmfVEP in 14 areas as a function of temporal frequency. Mean values and error bars (95 % CIs) represent results from nine subjects. The total number of 58 responses was averaged in groups as displayed in the *inset*. The two most nasal groups (area 11 and 12, including the nasal wings) are the average of 5 fields while the other 12 groups are averaged by 4 focal measurements. *Open symbols*: superior areas. *Filled symbols*: inferior areas. To calculate the SNR, the amplitude at reversal frequency was divided by the mean amplitude of nearest flanking non-stimulus frequencies (NL1 and NR1, see Fig. 3). Always,

the largest SNR value from six channels was chosen. Calculation of NNR used the same procedure on nine measurements. However, instead of using the amplitude at the reversal frequency, a randomly chosen non-stimulus neighbouring frequency was chosen (NR1 or NL1) and the amplitude was divided by the mean of two other adjacent non-stimulus amplitudes [i.e., NR1/mean(NL1,NR2) or NL1/mean(NL2,NR1)]. NNR was between 0.6 and 3.2 dB when the same ‘best of six’ method was used, as in calculation of SNR

Discussion

The aim of this study was to investigate whether the m-sequence technique and steady-state stimulation can be used to elicit reliable multifocal VEP responses. Here, we were able to show that a conventional monitor-based VEP system with the m-sequence technique can, indeed, be used to measure ssmfVEPs. We used frequencies that are technically realizable with our monitor system and found responses that were different from statistical noise in the frequency range between 7.5 and 10 Hz.

The first results in normal subjects suggest that significant differences between response and random noise can be achieved using a conventional dartboard spatial configuration. It was shown that amplitudes of the components at reversal frequency were correlated with the amplitudes as measured with a conventional long-term program (Fig. 1). In accordance with earlier steady-state measurements [27], amplitudes and the SNR of ssmfVEP showed a frequency tuning with a maximum near 9 Hz. Frequencies higher than 10 Hz showed a lower SNR and seem to be less suitable in the present setup. Electrophysiological recordings contain a response and simultaneous noise. In conventional mfVEP recordings of transient responses, separate signal and noise windows can be defined and the SNR can be calculated by the signal plus noise in the response window divided by the ‘pure’ noise in a temporally

separated noise window. Thus, the mean SNR in transient VEPs equals 1 when no stimulus reaction is present [13]. In studies with steady-state stimulation, it is possible to use amplitudes at the reversal frequency and flanking non-reversal frequencies for SNR calculation [25, 28]. Again, the SNR should be 1 when no response is present. Here we used the ratio of signal amplitude at the reversal frequency divided by the mean of two or of four neighbouring frequencies for calculations of the SNR. The strategy with four neighbours clearly resulted in smaller SNRs compared to when two neighbours were used and, therefore, was less satisfactory. In another steady-state VEP study by Vaegan et al. [29], it was suggested to determine the difference between response amplitude at the reversal frequency and the mean of non-signal amplitudes at other frequencies and to divide it by the standard deviation of the noise. In addition to the above described SNR techniques, we used this method on our measurements (data not shown). We were not able to show the benefit of this strategy in our data, possibly because of the low frequency resolution in our measurements.

In addition to electrical interference and disturbances due to subject’s movements, spontaneous brain activities contribute to noise. The frequencies used in the present steady-state stimulation sometimes were in the range of the alpha EEG [23, 30]. It is known that alpha EEGs are not always constant and can change their frequency in the

course of a day and during mental activity [16, 31, 32]. Assuming that IAF is constant during the measurements, the alpha activities could possibly have an impact on our measurements in two ways: either, the alpha EEG could have a high value at a non-stimulus neighbour frequency and, therefore, reduce the SNR, or the alpha EEG could be close to the reversal frequency and, therefore, interfering with the response and, thereby, altering the apparent SNR. As expected, the alpha frequencies of the present subjects were in the same range as some reversal frequencies of the ssmfVEPs. However, it can be assumed that alpha EEG in our ssmfVEP recordings are diminished due to averaging and due to decorrelation of alpha waves from the stimulus by repeating the measurements in different cycles. Furthermore it is known that alpha activities are much smaller in the presence of a visual input (i.e., the running text during stimulation) compared to closed eyes conditions. The running text is also meant to keep the subject alert during the measurements thereby reducing the amplitude of the alpha waves. When the IAF was close to the reversal frequency, the ssmfVEP is possibly composed of the response and the superimposed alpha waves and it can be assumed that the response at the reversal frequency might be changed [30] due to interference between the two [23]. To check if such interference, indeed, might have occurred, we included the IAF (*asterisk*) in all plots of Fig. 4. However, we did not notice any signs of the influence of the alpha waves on the response amplitudes or the SNR.

In those cases where the IAF is close to the right or left neighbouring frequency, the alpha activities might also affect the calculation of the SNR. To minimize a possible reduction of the SNR due to large alpha waves, we performed an analysis in which the noise component at the frequency closest to the IAF was excluded from the SNR calculation. In the mean SNRs (Fig. 5), the IAF exclusion did not result in larger SNR values than when the neighbouring frequencies were used. We conclude that alpha waves have little influence on the SNRs and, therefore, there is no need to exclude components at frequencies that are close to the IAF.

A known drawback of using small stimulus areas in mfVEP is that the SNR can be below the criterion for a significant response [12]. None of the nine subjects showed significant responses for all of the fields. A method to improve the SNR in mfVEP measurements is spatial integration or averaging of responses to neighbouring test positions, where similar results are expected. The advantage of this technique has been documented before [12, 30, 33]. Here, we used a very similar averaging of responses as suggested before [12]. After averaging, we found significant responses for all areas when considering the data from all nine subjects (Fig. 6). Considering individual results, the spatially averaged responses were significantly above noise for most locations. 5 subjects showed SNR values

above noise for all 14 locations. However, the responses were not significantly above noise for areas 12, 13 and 14 in 4 subjects. This is in agreement with the results of earlier studies [8, 34] where lower amplitudes in these areas were found. We used the electrode configuration as suggested by the manufacturers of the equipment. Mounting four electrodes around theinion and the evaluation of six channels has proven to be useful in the detection of the conventional long-term mfVEP measurements [2, 6, 13]. Similarly, the present data showed that maximal SNRs can be found in any one of the six channels. For improvement of the SNR, in future studies with the steady-state technique, the benefit of additional (e.g., forehead) electrodes [28, 35] [12] should be investigated. Using such electrode setups, the combined evaluation of orthogonal signals (Euclidian sum) might reveal larger SNRs than any single channel [29]. In addition to possible improvement of spectral analysis and electrode configuration, future studies could be performed with different numbers of reversals in all fields. Here, we have arbitrarily chosen four reversals per m-step in order to achieve similar durations in the ssmfVEP and conventional mfVEP measurements. However, longer traces and larger numbers of local pattern reversals might be advantageous to minimizing the bias from trend artefacts [36]. Meigen and Bach [25] discussed constraints for SNR determination in ophthalmological steady-state measurements and recommended signal lengths exceeding 1 s. More repetitions will increase not only the frequency resolution and possibly the signal quality, but also the total recording time. Future measurements [37–39] could additionally include the variation of m-sequence length and study the value of cycle repetitions. The ssmfVEP may be useful for objective perimetry because spectral analyses can be used for automated evaluation of the responses. The steady-state measurements are possibly shorter for similar SNRs than conventional mfVEPs because the whole recording period is used for analysis, whereas in transient measurements, separate intervals for registration of signal response and noise are needed and because eye movements and electromyographic artefacts may be less disturbing in the analysis of ssmfVEP recordings [40, 41]. Furthermore, flickering targets in psychophysical perimetric tests are known to be superior to flashing stimuli in diagnosing certain diseases such as glaucoma. Therefore, ssmfVEP may also be a preferable method in diagnosing glaucoma. In this study, we evaluated amplitudes at stimulus and non-stimulus frequencies. We did not evaluate the phases nor the characteristics of higher harmonics. The analysis of transient responses may lead to a more comprehensive understanding of latencies between visual stimulation and response. More studies are needed, not only to optimise the stimulus conditions, but also to demonstrate higher diagnostic power than conventional procedures.

Comparison of the time for obtaining reliable results with this technique and with conventional mfVEP must be performed in order to prove the clinical usefulness of the smfVEP.

Compliance of ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

Funding No funding was received for this research.

References

- Baseler HA, Sutter EE, Klein SA, Carney T (1994) The topography of visual evoked response properties across the visual field. *Electroencephalogr Clin Neurophysiol* 90(1):65–81
- Klistorner A, Graham SL (2000) Objective perimetry in glaucoma. *Ophthalmology* 107(12):2283–2299
- Hood DC, Zhang X, Greenstein VC, Kangovi S, Odel JG, Liebmann JM, Ritch R (2000) An interocular comparison of the multifocal VEP: a possible technique for detecting local damage to the optic nerve. *Invest Ophthalmol Vis Sci* 41(6):1580–1587
- Hood DC, Odel JG, Zhang X (2000) Tracking the recovery of local optic nerve function after optic neuritis: a multifocal VEP study. *Invest Ophthalmol Vis Sci* 41(12):4032–4038
- Graham SL, Klistorner AI, Goldberg I (2005) Clinical application of objective perimetry using multifocal visual evoked potentials in glaucoma practice. *Arch Ophthalmol* 123(6):729–739
- Kaltwasser C, Horn FK, Kremers J, Juenemann A, Bergua A (2011) Objective visual field determination in forensic ophthalmology with an optimized 4-channel multifocal VEP perimetry system: a case report of a patient with retinitis pigmentosa. *Doc Ophthalmol* 123(2):121–125
- Alshowaier D, Yannikas C, Garrick R, Van Der Walt A, Graham SL, Fraser C, Klistorner A (2015) Multifocal VEP assessment of optic neuritis evolution. *Clin Neurophysiol* 126:1617–1623
- Horn FK, Kaltwasser C, Juenemann AG, Kremers J, Tomow RP (2012) Objective perimetry using a four-channel multifocal VEP system: correlation with conventional perimetry and thickness of the retinal nerve fibre layer. *Br J Ophthalmol* 96(4):554–559
- Punjabi OS, Stamper RL, Bostrom AG, Han Y, Lin SC (2008) Topographic comparison of the visual function on multifocal visual evoked potentials with optic nerve structure on Heidelberg retinal tomography. *Ophthalmology* 115(3):440–446
- Laron M, Cheng H, Zhang B, Schiffman JS, Tang RA, Frishman LJ (2010) Comparison of multifocal visual evoked potential, standard automated perimetry and optical coherence tomography in assessing visual pathway in multiple sclerosis patients. *Mult Scler* 16(4):412–426
- Klistorner AI, Graham SL, Grigg JR, Billson FA (1998) Multifocal topographic visual evoked potential: improving objective detection of local visual field defects. *Invest Ophthalmol Vis Sci* 39(6):937–950
- Hood DC, Zhang X, Hong JE, Chen CS (2002) Quantifying the benefits of additional channels of multifocal VEP recording. *Doc Ophthalmol* 104(3):303–320
- Hood DC, Greenstein VC (2003) Multifocal VEP and ganglion cell damage: applications and limitations for the study of glaucoma. *Prog Retin Eye Res* 22(2):201–251
- Mousa MF, Cubbidge RP, Al-Mansouri F, Bener A (2013) The role of hemifield sector analysis in multifocal visual evoked potential objective perimetry in the early detection of glaucomatous visual field defects. *Clin Ophthalmol* 7:843–858
- Lindenberg T, Peters A, Horn FK, Lausen B, Korth M (2004) Diagnostic value of multifocal VEP using cross-validation and noise reduction in glaucoma research. *Graefes Arch Clin Exp Ophthalmol* 242(5):361–367
- Zhang X, Hood DC, Chen CS, Hong JE (2002) A signal-to-noise analysis of multifocal VEP responses: an objective definition for poor records. *Doc Ophthalmol* 104(3):287–302
- Regan D (1989) *Human brain electrophysiology: evoked potentials and evoked magnetic fields in science and medicine*. Elsevier, New York
- Burkitt GR, Silberstein RB, Cadusch PJ, Wood AW (2000) Steady-state visual evoked potentials and travelling waves. *Clin Neurophysiol* 111(2):246–258
- Bakardjian H, Tanaka T, Cichocki A (2010) Optimization of SSVEP brain responses with application to eight-command brain-computer interface. *Neurosci Lett* 469(1):34–38
- Vialatte FB, Maurice M, Dauwels J, Cichocki A (2010) Steady-state visually evoked potentials: focus on essential paradigms and future perspectives. *Prog Neurobiol* 90(4):418–438
- Mandel C, Luth T, Laue T, Rofer T, Graser A, Krieg-Bruckner B (2009) Navigating a smart wheelchair with a brain-computer interface interpreting steady-state visual evoked potentials. *Proc Conf Rec IEEE/RSJ Int Conf Intell Robots Syst*, St Louis, MO: 1118–1125
- Abdullah SN, Vaegan BMY, Maddess T (2012) Contrast-response functions of the multifocal steady-state VEP (MSV). *Clin Neurophysiol* 123(9):1865–1871
- Herrmann CS (2001) Human EEG responses to 1–100 Hz flicker: resonance phenomena in visual cortex and their potential correlation to cognitive phenomena. *Exp Brain Res* 137(3–4):346–353
- Kaltwasser C, Horn FK, Kremers J, Juenemann A (2009) A comparison of the suitability of cathode ray tube (CRT) and liquid crystal display (LCD) monitors as visual stimulators in mfERG diagnostics. *Doc Ophthalmol* 118(3):179–189
- Meigen T, Bach M (1999) On the statistical significance of electrophysiological steady-state responses. *Doc Ophthalmol* 98(3):207–232
- Norcia AM, Tyler CW, Hamer RD, Wesemann W (1989) Measurement of spatial contrast sensitivity with the swept contrast VEP. *Vis Res* 29(5):627–637
- Lin FC, Zao JK, Tu KC, Wang Y, Huang YP, Chuang CW, Kuo HY, Chien YY, Chou CC, Jung TP (2012) SNR analysis of high-frequency steady-state visual evoked potentials from the foveal and extrafoveal regions of human retina. *Conf Proc IEEE Eng Med Biol Soc* 2012:1810–1814
- Vaegan, Elia MA, Zheng J (2007) Optimising steady-state sweep VEPs to stimuli like the central FDT target: comparison to psychophysical thresholds in early glaucoma detection. In: Marmor M, ed XLV ISCEV international symposium—scientific programme, hotel Taj Krishna, Banjara Hills, Hyderabad, India, August 25–29, 2007 *Doc Ophthalmol*; 115(suppl):12
- Vaegan RAMA, Sanderson GF (2008) Glaucoma affects steady-state VEP contrast thresholds before psychophysics. *Optom Vis Sci* 85(7):547–558
- Birca A, Carmant L, Lortie A, Lassonde M (2006) Interaction between the flash evoked SSVEPs and the spontaneous EEG activity in children and adults. *Clin Neurophysiol* 117(2):279–288
- Klimesch W (1999) EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. *Brain Res Brain Res Rev* 29(2–3):169–195
- Garn H, Waser M, Lechner M, Dorfer M, Grosseegger D (2012) Robust, automatic real-time monitoring of the time course of the individual alpha frequency in the time and frequency domain. *Conf Proc IEEE Eng Med Biol Soc* 2012:2227–2231

33. Klistorner AI, Graham SL (1999) Multifocal pattern VEP perimetry: analysis of sectoral waveforms. *Doc Ophthalmol* 98(2):183–196
34. Fortune B, Hood DC (2003) Conventional pattern-reversal VEPs are not equivalent to summed multifocal VEPs. *Investig Ophthalmol Vis Sci* 44(3):1364–1375
35. Bradnam MS, Montgomery DM, Evans AL, Keating D, McClure EA, Damato BE, McFadzean R (1996) Objective detection of hemifield and quadrantic field defects by visual evoked cortical potentials. *Br J Ophthalmol* 80(4):297–303
36. Bach M, Meigen T (1999) Do's and don'ts in fourier analysis of steady-state potentials. *Doc Ophthalmol* 99(1):69–82
37. Chen CS, Hood DC, Zhang X, Karam EZ, Liebmann JM, Ritch R, Thienprasiddhi P, Greenstein VC (2003) Repeat reliability of the multifocal visual evoked potential in normal and glaucomatous eyes. *J Glaucoma* 12(5):399–408
38. Fortune B, Demirel S, Zhang X, Hood DC, Johnson CA (2006) Repeatability of normal multifocal VEP: implications for detecting progression. *J Glaucoma* 15(2):131–141
39. Punjabi OS, Stamper RL, Bostrom AG, Lin SC (2008) Repeatability of the multifocal visual evoked potentials in a clinical glaucoma setting. *Can J Ophthalmol* 43(4):435–440
40. Perlstein WM, Cole MA, Larson M, Kelly K, Seignourel P, Keil A (2003) Steadystate visual evoked potentials reveal frontally-mediated working memory activity in humans. *Neurosci Lett* 342:191–195
41. Gray M, Kemp AH, Silberstein RB, Nathan PJ (2003) Cortical neurophysiology of anticipatory anxiety: an investigation utilizing steady-state probe topography (SSPT). *Neuroimage* 20:975–986