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Simulated nystagmus suppresses pattern-reversal but not pattern-onset visual evoked potentials

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Abstract

Objective: The aim of this study is to quantify and compare the effects of simulated horizontal nystagmus on pattern-reversal and pattern-onset visual evoked potentials (VEPs).

Methods: In eight visually normal subjects with normal oculomotor behaviour, we monitored eye movements and recorded pattern-reversal and pattern-onset VEPs from occipital electrodes. Subjects viewed the stimulus monocularly via a mirror, which was placed close to the eye and driven by a scanner at four different amplitudes (0, 1, 2, and 3°) with a 4 Hz saw-tooth waveform to simulate horizontal jerk-nystagmus.

Results: Retinal image motion nearly abolished the pattern-reversal VEPs (maximal reduction by 85%; mean reduction by 72%, $P < 0.001$), while there was a non-significant reduction (mean reduction by 15%) of the pattern-onset VEPs.

Conclusions: The differential effect of simulated nystagmus on pattern-reversal and pattern-onset VEPs resembles that reported in studies on nystagmus patients. We conclude that the interaction of retinal image motion with the stimulus is sufficient to explain the reduction of pattern-reversal VEPs in patients with nystagmus and propose simulated nystagmus as a useful tool to test the influence of nystagmus on the efficiency of VEP stimuli.

Significance: This study demonstrates how horizontal jerk-nystagmus can be simulated and suggests possible mechanisms by which nystagmus reduces VEP responses.

Keywords: Human; Visual cortex; Nystagmus; VEP; Pattern-onset; Pattern-reversal

1. Introduction

Pattern-reversal stimulation is an important tool for the assessment of visual function with cortical visually evoked potentials (VEPs; Odom et al., 2004). However, in patients with oculomotor instabilities such as nystagmus, pattern-reversal responses are degraded to a degree, which severely confounds VEP interpretation (Creel et al., 1981; Kriss et al., 1992; Rosenberg and Bahman, 1987; Zubcov et al., 1991). This motivated the use of different stimulation modes, and indeed, sizable pattern-onset responses are often obtained in nystagmus patients (Apkarian and Shallo-Hoffmann, 1991; Apkarian et al., 1983; Saunders et al., 1998). The differential effect of nystagmus on VEP responses is surprising, and the underlying mechanisms have not yet been identified. Two main hypotheses can be distinguished. Firstly, there might be a stimulus dependent enhancement of nystagmus amplitudes specific for the disturbed optokinetic system of nystagmus patients (Dell'Osso, 1982; Kommerell, 1982, 1986). In this case, the residual motion energy of a pattern-reversal stimulus is believed to enhance involuntary eye movements while a pattern-onset stimulus with little or no such motion-energy will leave eye-movements unaffected. Thus, pattern-reversal responses would be selectively reduced in subjects with nystagmus. Secondly, the pattern-reversal stimulus might interact with the nystagmus-induced retinal image motion in a way that leads to a selective reduction of the pattern-reversal VEP. Various mechanisms might mediate such an interaction (extinction of the actual contrast reversal, motion smear, and motion adaptation, as detailed in Section 5). There is an experimental way to

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differentiate between these two hypotheses: the superimposition of retinal image motion onto the VEP stimulus in normal subjects, i.e. without nystagmus, should exert a differential effect on pattern-reversal and pattern-onset responses, if the 'oculomotor-hypothesis', outlined above, is invalid.

In the present study, we simulated horizontal jerk-nystagmus in normal subjects by superimposing nystagmus-like retinal image motion onto the pattern-reversal and pattern-onset stimuli during VEP recordings. Such an approach has the benefit to directly compare conditions with different degrees of simulated nystagmus amplitudes to a reference condition without any nystagmus in the same subject. Thus, we tested whether nystagmus-like retinal image motion affects VEP responses in subjects without real nystagmus in the same differential manner as has previously been demonstrated in nystagmus patients. This would not only demonstrate that the interaction between retinal image motion and the stimulus time course are sufficient to explain the selective reduction of pattern-reversal VEPs, it would also indicate that induced retinal image motion is a valid model that allows us to screen a variety of VEP stimuli for their use in nystagmus patients.

2. Methods

2.1. Subjects

Eight subjects aged 18–35 years with normal visual acuity gave their informed written consent prior to the study. The procedures followed the tenets of the declaration of Helsinki (World Medical Association, 2000) and the protocol was approved by the ethics committee of the University of Freiburg, Germany.

During the experiments, subjects viewed the stimulus with their left eye via a first-surface mirror (as detailed in Sections 2.2 and 2.2.3), while their right eye was patched. They were instructed to rest their gaze in the centre of the stimulus pattern and to focus on the pattern.

2.2. Stimulation

Stimuli were generated by a Power Macintosh G4 with a program based on the Apple Game sprockets (Bach, 1999) and presented on a CRT with a frame rate of 75 Hz.

2.2.1. Spatial stimulus characteristics

In accordance with the VEP standard (Odom et al., 2004), black-and-white checkerboard patterns with either of two check sizes, 0.25 and 1° of visual angle were tested. The pattern had a mean luminance of 27 cd/m^2, 98% contrast, and a horizontal and vertical extent of 26 and 21°, respectively. Subjects viewed the stimulus via a first-surface mirror that was placed at a distance of 10 cm from their eye and at a distance of 25 cm from the CRT, resulting in a total viewing distance of 35 cm.

2.2.2. Temporal stimulus characteristics

Two stimulation modes were tested: pattern-reversal (one reversal per 493 ms) and pattern-onset stimulation (ON for 40 ms; OFF for 440 ms). For pattern-onset, an onset epoch of 40 ms was chosen as this corresponds to the integration time for checkerboard onset and gives the largest responses (Jeffreys and Axford, 1972; Spekreijse et al., 1973) and as the same value has previously been used in VEP studies on nystagmus-patients (Apkarian and Shallo-Hoffmann, 1991). In the VEP literature, it is a common practice to refer to both pattern-onset and brief pattern-onset stimulation as pattern-onset, although the latter should in fact be referred to as 'pattern-pulse'. Throughout this article, we will adhere to the established terminology and refer to brief pattern-onset, i.e. pattern-pulse, simply as pattern-onset.

2.2.3. Simulation of nystagmus

We simulated horizontal jerk-nystagmus by oscillating a first-surface mirror in front of the subjects' eye around the vertical axis. Such an approach has been used in previous psychophysical studies, which demonstrated a similar effect of simulated and genuine nystagmus on visual acuity (Chung and Bedell, 1997; Ukwade and Bedell, 1999). Mirror motion was induced by a scanner (Scanner Control CCX 01; General Scanning Inc.), which controlled the mirror. The input signal for the scanner-mirror was generated with IGOR (Wavemetrics, Inc.) by a Power Macintosh G4 and converted to an analogue signal via the audio output. The use of the audio output was possible due to the low time constant of the audio-out high-pass filter. The mirror moved with a saw-tooth time-course of an amplitude of either 0, 1, 2, or 3° of visual angle as calibrated psychophysically within an error of 10%. During VEP recordings, the mirror moved at a frequency of 4 Hz as this is typical for idiopathic congenital nystagmus (Abadi and Worfolk, 1989; Bedell and Loshin, 1991; Yee et al., 1976). It should be noted that the frequency was incommensurable with the stimulation rate, i.e. not a multiple. Over the entire time course of the VEP recordings, there is, consequently, no time-locked relationship of stimulus onset and any particular phase of the mirror movement. This is important as it excludes the possibility that responses to any particular phase of mirror motion are extracted from the electroencephalogram during the averaging process, which eventually yields the VEP.

3. Electrophysiological recordings

3.1. VEP recordings

Electrodes were placed and labelled according to the international 10–20 System (American Encephalographic

Society, 1994). Potentials were recorded from three scalp electrodes referenced to F_z: Oz (occipital pole), PO_7, and PO_8. The ground electrode was attached to the right wrist. VEPs were averaged over at least 176 trials for each stimulus condition. Signals were amplified, filtered (first-order bandpass, 0.3–70 Hz, Toennies 'Physiologic Amplifier'), and digitized to a resolution of 12 bits at a sampling frequency of 1 kHz with a Macintosh 7200 computer. Using LabView (National Instruments), signals were 'streamed to disk' and also averaged on-line to monitor the recording.

3.2. EOG-recordings

We recorded the horizontal electro-oculogram (EOG) bitemporally to monitor eye movements and the vertical EOG of the left eye for blink detection. EOGs were amplified, and digitized at a sampling rate of 1000 Hz. The horizontal EOG was calibrated just before the beginning of the VEP recordings.

3.3. Data-analysis

3.3.1. VEP analysis

Trials were analysed off-line with Igor Pro (Wavemetrics, Inc.) for an interval that began 100 ms prior to stimulus onset and ended 400 ms after stimulus onset. Trials with blinks, detected with a threshold criterion of 100 μV, were discarded. Sweeps were pooled according to stimulus conditions and digitally filtered (0–40 Hz) before averaging. The zero level was defined as the mean value of the averaged trace from 100 ms before to 70 ms after stimulus onset and used as reference for peak measurements.

3.3.2. EOG analysis

For the quantification of the impact of simulated nystagmus on eye-movements, the EOG recordings were Fourier-analysed which allowed the assessment of the EOG amplitude at the fundamental frequency of the mirror-movement and at the fundamental frequency of the stimulus. The content of the fundamental frequency of the mirror-movement in the EOG recording was analysed over a 10 s window, resulting in a frequency resolution of 0.1 Hz, the content of the fundamental frequency of the stimulus in the EOG was analysed over a 37 s window, resulting in a frequency resolution of 0.03 Hz. In all cases, the analysis epochs comprised an exact integer number of mirror- and stimulus-periods, respectively, to avoid overspill onto neighbouring frequencies (Bach and Meigen, 1999); this also obviates the use of a window function.

3.4. Procedure

An entire recording session lasted around 2 h, including preparation and breaks. Overall, 16 stimulus conditions were tested, i.e. two stimulation modes (pattern-onset/pattern-reversal), four mirror-amplitudes (0, 1, 2, and, 3°), and two check sizes (1 and 0.25°). The session was split into two halves. During the first part stimulus check size was 1°, during the second half 0.25°. Stimuli were presented in short blocks of 120 trials, lasting about 80 s. For each stimulus condition a total of 240 trials were presented, leaving at least 176 artefact-free trials as determined with a threshold criterion (see above, VEP-Analysis). VEP recordings started with a presentation of a pattern-reversal and pattern-onset block at a mirror-amplitude of 0°. Then these blocks were repeated with the next-higher mirror amplitude. Once an amplitude of 3° was reached, there was a break for the subject to recover from any adaptation and fatigue effects. Finally, the entire sequence was repeated with an inverted sequence of pattern-reversal and pattern-onset blocks. This design was chosen to avoid overspill of any adaptation effects from mirror motion into blocks with smaller or no mirror motion.

3.5. Analysis and statistics

To test the significance of the effect of simulated nystagmus on response amplitude, a peak analysis of the individual traces of each subject was performed. Univariate ANOVAs were applied to the logarithmised amplitude differences of P1–N2 for pattern-reversal and CIII–CII for pattern-onset responses. The Student-Newman-Keuls test was used for post-hoc testing of significances.

4. Results

4.1. Effect of simulated nystagmus on pattern-reversal and pattern-onset VEPs

For a qualitative assessment of the effects, the grand mean traces are depicted for each recording site, both stimulation modes, and all four amplitudes of retinal image motion in Fig. 1. Fig. 1(a) and (b) show the results for 1 and 0.25° checks, respectively. The various VEP components—N1, P1, and N2 for pattern-reversal and CI, CII, and CIII for pattern-onset-are indicated in Fig. 1. Fig. 1 shows that pattern-reversal responses are strongly reduced by retinal image motion even of small extent, i.e. 1°, while pattern-onset responses are little or not affected. These effects can be observed at all of the three recording sites and are also evident in the original VEP traces of the individual subjects. A quantitative account of these features is given in Fig. 2(a) and (b), for 1 and 0.25° check size, respectively, and in Table 1. The individual peak differences, P1–N2 for pattern-reversal and CIII–CII for pattern-onset, were determined in the individual VEP traces of each single subject, subsequently, averaged across subjects, and plotted as a function of simulated nystagmus amplitude. The same trends as for the grand mean traces depicted in Fig. 1 are evident: pattern-reversal responses are significantly affected by simulated nystagmus (mean reduction across both check

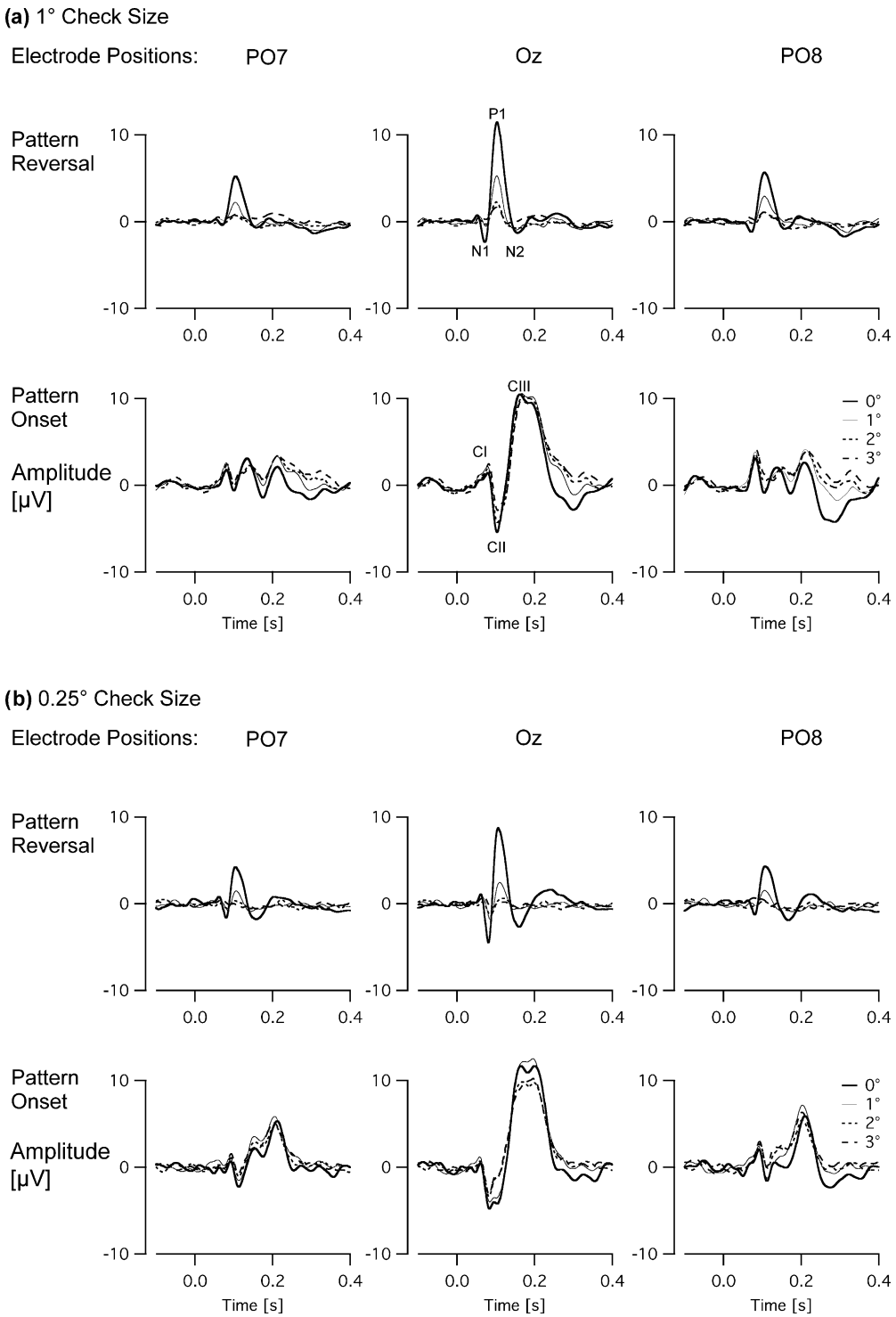

Fig. 1. Grand mean VEP traces (eight subjects) at three derivations for different degrees of simulated nystagmus. The typical main components of the pattern-reversal VEP (N1, P1, N2) and of the pattern-onset VEP (CI, CII, CIII) are indicated. Pattern-reversal responses are severely affected by small amplitudes, i.e. 1°, of simulated nystagmus, while there is only little effect on pattern-onset responses even at high amplitudes of simulated nystagmus, i.e. 3°. This holds for both check sizes (see (a) and (b)).

sizes and all three mirror amplitudes by 72%; $P < 0.001$, Table 1), while the effect on pattern-onset responses does not reach significance (mean reduction across check sizes and mirror amplitudes by 15%; $P > 0.22$). Note that there is not even a slight indication of an effect of 1° simulated nystagmus on pattern-onset responses, while pattern-reversal responses are already significantly affected at this level of simulated nystagmus (Fig. 2) as revealed by post hoc testing of pattern-reversal responses: for 1° check size all possible pair-wise differences between mirror amplitude

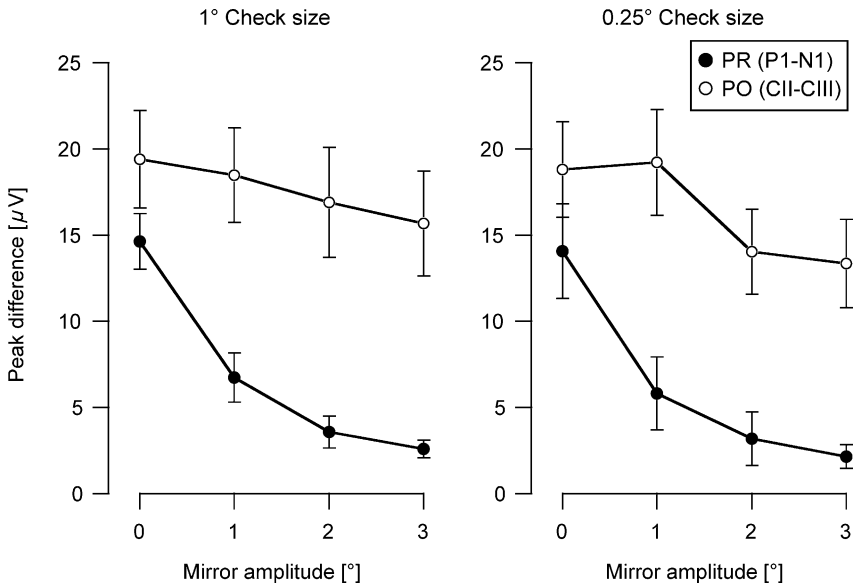

Fig. 2. Dependence of the VEP responses recorded at Oz on the amplitude of simulated nystagmus ($n = 8$; mean ± SEM). The amplitude differences of the most prominent peaks [N1 and P1 for pattern-reversal (PR) and CII and CIII for pattern-onset stimulation (PO)] are depicted. It is evident that pattern-reversal responses are severely affected by simulated nystagmus while pattern-onset responses are not or only little affected.

conditions were significant at a 5% level, for 0.25° check size all differences to the 0° mirror-amplitude conditions were significant at this level.

4.2. Effect of simulated nystagmus on eye-movements during visual stimulation

Simultaneous recordings of VEP and EOG enabled us to assess whether simulated nystagmus induces eye movements. Inspection of the EOG traces revealed that the mirror-excursions disturbed the fixation stability. They induced jerk-nystagmus-like eye movements during pattern-onset stimulation and square-wave jerks during pattern-reversal stimulation. These induced fixation instabilities had a maximal amplitude of approximately 1° for mirror-excursions of 3°, which was observed in a single subject with very pronounced fixation instabilities. Fourier analysis did not reveal a specific enhancement neither at the fundamental frequency of the stimulus nor at the mirror-frequency. The latter is depicted in Fig. 3: for each subject and stimulus condition a 10 s interval was analysed to quantify the impact of simulated nystagmus. EOG data were Fourier analysed and the signal amplitude at the fundamental frequency of the mirror-movement, i.e. 4 Hz, was extracted. In addition, eye movements were recorded for a control condition in four out of the eight subjects of this study to demonstrate that eye movements induced by mirror movements could be successfully detected with EOG recordings. Here, the mirror moved with 3° amplitude at comparatively low frequency of 1 Hz which is sufficiently slow to allow the subjects pursuit eye movements. In this condition, in contrast to the other stimulus conditions, subjects were asked to pursue a fixation spot, which was reflected by the mirror, and hence moved at a frequency of 1 Hz. A Fourier analysis was performed to extract the signal amplitude at 1 Hz. The results given in Fig. 3 demonstrate that mirror-induced eye movements can clearly be detected with the EOG recordings (right panel, notice response in the spectrum at 1 Hz). Mirror movements at 4 Hz, however, do not induce any systematic oculomotor response (left and middle panels of Fig. 3).

5. Discussion

We report a significant reduction of pattern-reversal responses by around 70% due to simulated 4 Hz nystagmus of 1–3° amplitude. In contrast, we did not observe a significant effect of simulated nystagmus on pattern-onset

Table 1
Dependence of VEP amplitudes on mirror excursion amplitude

Check size	1°		0.25°	
VEP response (%):	Reversal	Onset	Reversal	Onset
Mirror amplitude (°)				
1	46	95	41	102
2	25	87	23	75
3	18	81	15	71
P-value	<0.0001	0.85	<0.001	0.22
F-value; DF	13.93; 3	0.273; 3	8.269; 3	1.547; 3

The averaged ($n = 8$) peak differences (P1–N2 and CIII–C2 for pattern reversal and pattern onset stimulation, respectively) for three different mirror amplitudes are given as a percentage of the amplitude difference obtained for the control condition, i.e. 0° mirror motion. Pattern-reversal and pattern-onset stimulation modes were tested for two different check sizes. Details of ANOVAs (*P*-value, *F*-values, and degrees of freedom (DF)) to test the significance of the dependence of peak difference on mirror-amplitude are given in the two bottom rows.

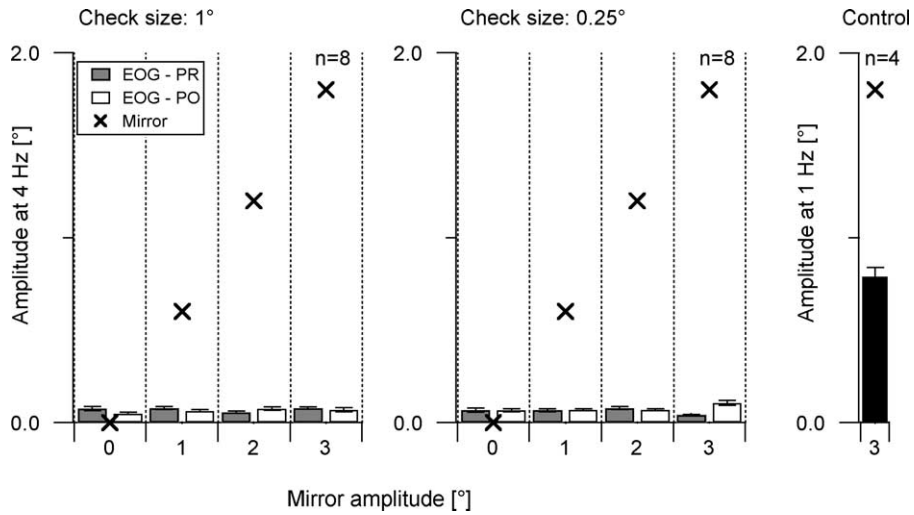

Fig. 3. Quantification of the nystagmus due to mirror-motion induced retinal image motion (mean ± SEM). The EOG-traces were Fourier analysed and the amplitude at the mirror oscillation-frequency (4 Hz) was assessed for both check sizes and stimulation modes (PR, pattern reversal; PO, pattern onset), and for all four amplitudes of simulated nystagmus. For comparison, the amplitude of the mirror motion at 4 Hz is indicated (crosses). It is evident that there is no systematic effect of mirror motion on the EOG and all responses are around noise level. The right panel depicts a control condition to demonstrate that mirror induced eye-movements can be detected with our analysis: The mirror moved at only 1 Hz (3° amplitude) to enable the subjects to track the movement of the mirror and the subjects were instructed to follow the image. Here, a strong signal was detected with the EOG.

responses. This demonstration of the robustness of pattern-onset VEPs to simulated nystagmus corresponds well to previous reports in the literature on pattern-onset VEPs in nystagmus patients (Apkarian and Shallo-Hoffmann, 1991; Creel et al., 1981; Kriss et al., 1992; Rosenberg and Bahman, 1987; Saunders et al., 1998; Zubcov et al., 1991). It is concluded that the superposition of retinal image motion onto VEP stimuli is a valid paradigm to investigate the mechanisms underlying VEP degradation during nystagmus and to test the efficiency of VEP stimuli for nystagmus patients.

The present study is the first to show that the suppression of pattern-reversal VEPs during nystagmus-like image motion is not specific to nystagmus patients, but simply due to the retinal image motion induced by nystagmus. The differential effect of nystagmus on VEP responses does therefore not depend on specific characteristics of the visual system of nystagmus patients, such as a disturbed optokinetic system (Dell'Osso, 1982; Kommerell, 1982, 1986) or altered visual pathways (Apkarian et al., 1983; Hoffmann et al., 2003b). The interaction of the induced retinal image motion with the VEP stimulus appears to be sufficient to explain differential VEP degradation. Retinal image motion might exert its effect on pattern-reversal VEPs via one of three mechanisms: (a) Partial cancellation of the contrast reversal due to the shift of the pattern immediately before pattern-reversal: If the retinal image is shifted by an entire check in between the reversals of a pattern-reversal stimulus, contrast reversals cancel out and no response to such a stimulus should be expected. In contrast, a pattern-onset response would not be reduced by such a mechanism, as the phase of the pattern cannot influence the pattern-onset response. Although this is a plausible mechanism at first sight, it is unlikely to quantitatively explain the differential effect of retinal image motion on the different stimulus modes: In the present study, during the slow phase of simulated nystagmus, the maximal retinal image displacement within a single frame is 3/75°, i.e. a 1/6 of a 0.25° check and a 1/25 of a 1° check. Consequently, the pattern-reversal will not be cancelled out and only small effects should be the result of retinal image displacement. (b) Reduction of retinal contrast induced by motion smear: image contrast is reduced by retinal image motion. While this should be expected to affect pattern-reversal and pattern-onset responses similarly, one might hypothesize that grossly differing contrast response functions of pattern-reversal and pattern-onset responses might result in the observed differential effect of retinal image motion. Therefore, this possibility cannot be entirely excluded. (c) Amplitude reduction due to motion adaptation induced by the continuous retinal image motion: Nystagmus-induced retinal image motion of the stimulus pattern is likely to cause motion adaptation and it is well known that motion adaptation exerts a great influence on VEP amplitudes (Bach and Ullrich, 1994; Heinrich and Bach, 2001; Hoffmann et al., 1999). Interestingly, pattern-reversal and pattern-onset stimulation differ in the interval for which a pattern, which can adapt the visual system, is present (100% vs. 12% of the interval, respectively). Thus, pattern-onset stimulation has a lower potential by far to drive adaptation during retinal image motion than pattern-reversal stimulation. Consequently, motion adaptation is a likely candidate to explain the differential effect of nystagmus on pattern-reversal and pattern-onset responses. It should be noted that induced retinal image motion did cause fixation instabilities during the reported VEP recordings. These eye-movements might enhance the degrading effect of the above mechanisms on pattern-reversal VEP responses.

We introduced a paradigm to study the mechanisms underlying the degradation of VEPs during nystagmus quantitatively and demonstrated a small effect of retinal image motion on pattern-onset compared to pattern-reversal VEPs. Pattern-onset stimulation might, therefore, be of great clinical relevance in patients with nystagmus. This has already been demonstrated for the detection of visual pathway-abnormalities (Apkarian, 1996; Apkarian and Shallo-Hoffmann, 1991) and it is promising to test the potential of pattern-onset VEPs for the clinical diagnosis of other aspects of visual function in patients with nystagmus. Furthermore, it should be clarified whether pattern-onset stimulation in nystagmus patients is not only preferable for transient, but also for steady-state and multifocal VEPs (Hood and Greenstein, 2003). The latter is particularly intriguing as pattern-onset stimulation has recently been demonstrated to be a powerful tool for the recording of mfVEPs (Hoffmann et al., 2003a; James, 2003). The 'simulated nystagmus paradigm' provides an adequate tool to resolve these issues.

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