

# Simulated nystagmus reduces pattern-reversal more strongly than pattern-onset multifocal visual evoked potentials

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## Abstract

**Objective:** In patients with nystagmus conventional pattern-reversal visual evoked potentials are severely degraded, while sizeable pattern-onset VEPs can often still be obtained. We tested whether this differential effect of retinal image motion on pattern-reversal and pattern-onset responses also applies to multifocal VEPs (mfVEPs).

**Methods:** In eight subjects with normal oculomotor behaviour and vision we recorded pattern-reversal and pattern-onset mfVEPs from an occipital electrode pair to 60 locations of a scaled dartboard-pattern, and to 64 locations of a uniform checkerboard-pattern. Subjects viewed the stimulus monocularly via a mirror, which was placed close to the eye and driven by a scanner with a 4 Hz sawtooth waveform at an amplitude of 2° to simulate horizontal jerk nystagmus and of 0° for the reference condition.

**Results:** For the scaled dartboard-stimulus we observed an eccentricity-dependent effect of induced retinal image motion on mfVEP responses: in the central visual field (0–0.5°), pattern-reversal and pattern-onset responses were reduced by 73 and 42%, respectively. In the periphery (10–16°), only pattern-reversal responses were reduced (by 27%), while pattern-onset responses were enhanced by 39%. Pattern-onset responses to the uniform checkerboard stimulus were enhanced by 17%, while pattern-reversal responses were reduced by 27%.

**Conclusions:** Pattern-onset mfVEPs are more efficient than pattern-reversal mfVEPs, if retinal image motion is superimposed onto the stimulus. This is in close correspondence to previous reports on conventional VEPs.

**Significance:** This study demonstrates a differential effect of retinal image motion on pattern-reversal and pattern-onset mfVEPs and thus suggests stimulus conditions to enhance the efficiency of mfVEP recordings in patients with moderate nystagmus.

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## 1. Introduction

Multifocal visual evoked potentials (mfVEPs) enable us to record, within a short time interval, cortical responses from a great number of distinct visual field locations. Therefore they provide a powerful tool to screen the visual field for abnormal or missing representations on the visual cortex (Baseler et al., 1994; Hood and Greenstein, 2003; Klistorner et al., 1998; Sutter, 1991). The use of mfVEPs is complicated by the convolution of the cortex, which results in a great intersubject variability of the responses and in

false alarms in the detection of scotomas (Baseler et al., 1994; Hood et al., 2000a). Multielectrode-recordings (Hood et al., 2002; Klistorner and Graham, 2000), interocular comparison of the responses (Graham et al., 2000; Hood et al., 2000b), and refined analysis strategies (Goldberg et al., 2002; Hood et al., 2003; Zhang et al., 2002) have helped us to overcome these difficulties and have thus opened the possibility to use mfVEPs as a routine tool for the objective assessment of cortical representations of the visual field.

While mfVEPs recorded to pattern-reversal stimulation emerged from the optimisation process outlined above, some studies drew attention to mfVEPs recorded to pattern-onset stimuli (Hoffmann et al., 2003a; James, 2003). Interestingly, a possible target of pattern-onset mfVEPs might be patients

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with instable fixation: all previous mfVEP studies addressed patient groups with stable fixation and it is unknown whether it is possible to obtain sizable mfVEPs in patients with moderate nystagmus. Studies using conventional transient VEPs (cVEPs), showed that pattern-onset responses can still be obtained during genuine or simulated nystagmus while pattern-reversal responses are severely degraded or even absent under such conditions (Apkarian and Shallo-Hoffmann, 1991; Apkarian et al., 1983; Creel et al., 1981; Hoffmann et al., 2004; Saunders et al., 1998). Pattern-onset cVEPs thus opened the possibility to identify visual pathway abnormalities in patients with nystagmus (e.g. albinism, Apkarian et al., 1983). These abnormalities affect only part of the visual field (Hoffmann et al., 2003b) and the use of mfVEPs might allow one to describe the visual field topography of such visual pathway abnormalities.

It is unknown, at present, whether the differential effect of nystagmus on pattern-reversal and pattern-onset cVEPs also applies to VEP responses obtained during multifocal stimulation, i.e. whether multifocal pattern-onset stimulation might be more efficient in patients with moderate nystagmus than pattern-reversal stimulation. We addressed this issue by recording mfVEPs to pattern-reversal and pattern-onset in subjects with normal vision and normal oculomotor behaviour while we superimposed retinal image motion, which mimics the effect of horizontal jerk-nystagmus, onto the stimuli. Simulating nystagmus has the benefit that conditions with nystagmus-like retinal image motion can be compared to reference conditions without nystagmus within the same subject and it has recently been shown for cVEPs that the effect of horizontal jerk-nystagmus on VEPs can be simulated by such a superposition of retinal image motion onto the stimuli (Hoffmann et al., 2004).

## 2. Methods

We conducted two experiments with the same methods except the stimulus layout used and part of the sample of volunteers that participated. In both experiments we used pattern-reversal and pattern-onset stimulation.

### 2.1. Subjects

Eight subjects aged either 21–28 years (experiment 1) or 22–29 years (experiment 2) 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 ‘Stimulation’ and ‘Simulation of nystagmus’), 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

VERIS 4.8 (EDI: Electro-Diagnostic Imaging, San Mateo, CA) was used for stimulus delivery and electrophysiological recordings.

#### 2.2.1. Temporal stimulus characteristics

Stimuli were presented on a computer monitor driven with a frame rate of 75 Hz. The stimulus display was subdivided into individual fields, which were stimulated independently according to an m-sequence with  $2^{15}-1$  elements for pattern-reversal stimulation and  $2^{14}-1$  elements for pattern-onset stimulation. M-sequences consist of a pseudo-random succession of 0 and 1 states. For pattern-reversal stimulation these two states were represented by two contrast inverted checkerboard fields (see Fig. 1A). For pattern-onset stimulation state 0 was represented by a succession of two grey fields, while state 1 was represented by a succession of a checkerboard-pattern and a grey field (see Fig. 1B). Due to this difference in the time-course of stimulation, pattern-reversal responses can be extracted as the first slice of the 2nd order kernel response, while pattern-onset responses can be extracted as the 1st order kernel response. Each pattern or field appears for a single frame period. Therefore, the states last twice as long for pattern-onset stimulation than for pattern-reversal stimulation, as pattern-onset/offset comprises a frame of pattern *plus* a frame of uniform grey for the elemental state. To achieve the same duration of the recording sessions for both stimulation modes, we used an m-sequence half as long for pattern-onset as for pattern-reversal stimulation resulting in a duration of a single block of about 7 min. The blocks were broken up into 16 overlapping segments each lasting about 27 s.

Choosing equal durations of pattern-reversal and pattern-onset recordings helps to assess which stimulus might be more efficient in the presence of retinal image slip. On the other hand, it will cause only half of the trials, which enter the analysis for pattern-reversal stimulation, to enter the analysis for pattern-onset stimulation and will thus reduce the signal-to-noise-ratio for pattern-onset responses relative to pattern-reversal responses. To check that this does not bias the results, we performed the analyses also with only half of the acquired pattern-reversal trials and obtained effects of mirror-motion on pattern-reversal responses similar to those observed for the full data-set.

#### 2.2.2. Spatial stimulus characteristics

In Experiment 1, the stimulus display, a circular dartboard-pattern (Fig. 1A; mean luminance 31 cd/m<sup>2</sup>; contrast 98%), was viewed from a distance of 42.5 cm and covered 32° of visual angle. Sixty fields of this display were stimulated independently according to an m-sequence.

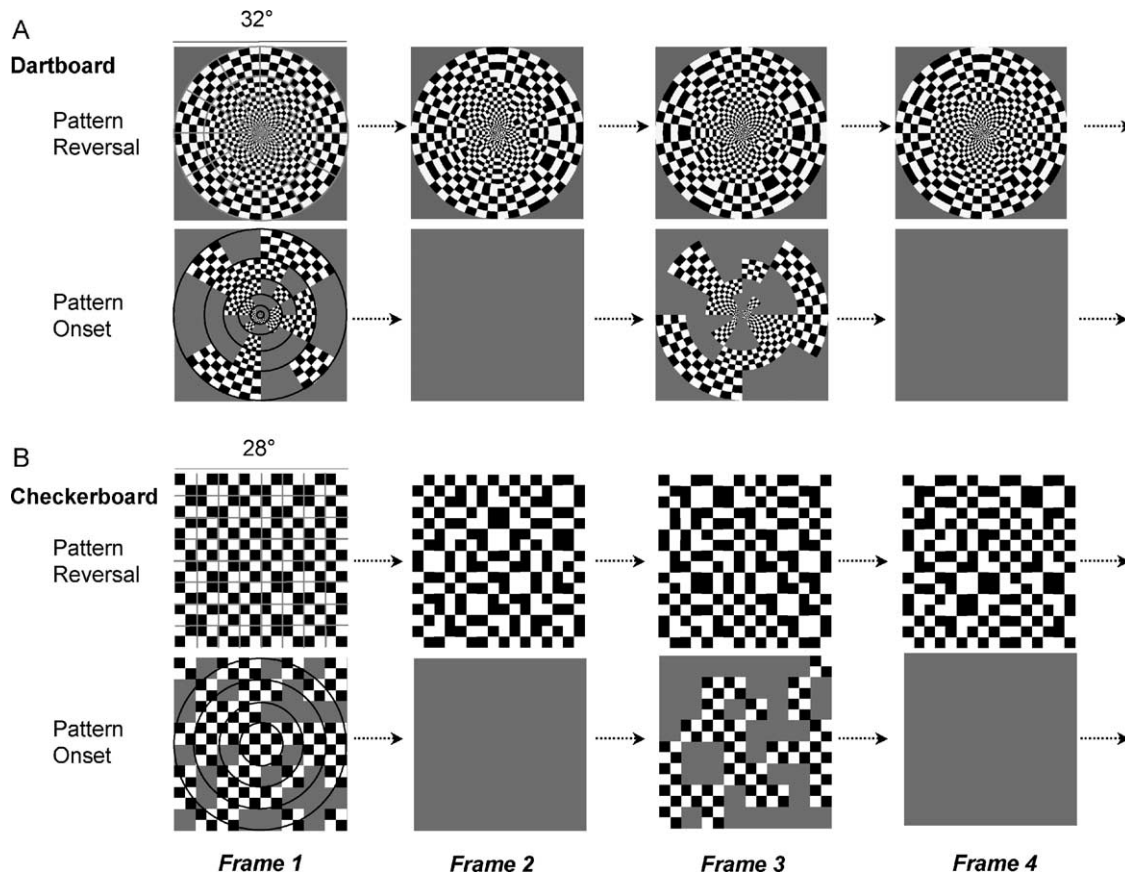


Fig. 1. Schematic of spatial and temporal stimulus characteristics for the scaled dartboard-pattern (A) and the uniform checkerboard-pattern (B) used. Pattern-reversal and pattern-onset time-courses are indicated in the top and bottom rows, respectively. In the leftmost column there is an indication of the individual visual field locations stimulated (top rows, in grey) and of the iso-eccentricity ranges used for subsequent analysis (bottom rows, in black).

Each field comprised a checkerboard consisting of  $4 \times 4$  checks. The radial extent of the fields was scaled with eccentricity from  $0.5^\circ$  in the centre to  $6^\circ$  in the periphery.

In Experiment 2, the stimulus display, a uniform isotropic checkerboard pattern (Fig. 1B; mean luminance  $31 \text{ cd/m}^2$ ; contrast 98%), was viewed from a distance of 48 cm and covered  $28^\circ$  of visual angle. Sixty four fields of this display were stimulated independently according to an m-sequence. Each field comprised a checkerboard consisting of  $2 \times 2$  checks, spanning a visual angle of  $3.5^\circ$ . The fields were *not* scaled with eccentricity. The rather large check size of  $1.75^\circ$  was chosen to guarantee that this stimulus can also be resolved in potential future patient groups, such as patients with foveal hypoplasia and consequently poor visual acuity (Pieh et al., 2005). In pilot experiments on normal controls we did not observe a prominent difference between responses to  $0.875$  and  $1.75^\circ$  checks.

### 2.2.3. Simulation of nystagmus

We simulated horizontal jerk-nystagmus by oscillating a first-surface mirror in front of the subject's eye around the vertical axis. Such an approach has been used previously: in psychophysical studies, which demonstrated a similar effect of simulated and genuine nystagmus on visual acuity

(Chung and Bedell, 1997; Ukwade and Bedell, 1999); in a recent electrophysiological study (Hoffmann et al., 2004), which demonstrated a similar differential effect of simulated nystagmus on pattern-reversal and pattern-onset cVEPs as that reported for nystagmus patients. 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 (Wave-metrics, Inc.) by a Power Macintosh G4 and converted to an analogue signal via the audio output. This was possible as the audio-out high-pass filter had a low time-constant. The mirror moved with a saw-tooth time-course of either  $0$  or  $2^\circ$  of visual angle as calibrated psychophysically within an error of 10%. It moved at a frequency of 4 Hz, as this is a frequency which is typical for idiopathic congenital nystagmus (Abadi and Worfolk, 1989; Bedell and Loshin, 1991; Yee et al., 1976). The size of the mirror and the stimulus pattern were matched to ensure that the entire stimulus was visible during each phase of the mirror-movement.

### 2.3. Electrophysiological recordings

mfVEPs were recorded with a gold cup electrode placed 4 cm above and referenced to the inion. The EEG was

amplified with a physiological amplifier (Toennies), band-pass filtered (low and high frequency cutoffs: 3 and 70 Hz), and digitised at 1200 Hz.

#### 2.4. Analysis and statistics

First and second order kernels for pattern-onset and pattern-reversal stimulation, respectively, were extracted using VERIS 4.8 (EDI, Inc). Spatial smoothing and artefact rejection features available in VERIS were not used. All subsequent analysis was performed with IGOR 5.0 (Wave-Metrics, Inc.). The traces were digitally low-pass filtered with a high frequency cut-off of 30 Hz.

To assess signal presence we evaluated the signal-to-noise ratio (SNR) as described by Zhang et al. (2002) using a ‘mean noise-window SNR’. First, the records from the two blocks for each stimulus were averaged. Then the SNR for each  $i$ th sector (of the  $n=60$  total sectors) of subject  $j$  was defined as

$$\text{SNR}_{ij} = \text{RMS}_{ij}(45 \text{ to } 150 \text{ ms}) / [\sum_i \text{RMS}_{ij}(325 \text{ to } 430 \text{ ms}) / n] - 1 \quad (1)$$

The denominator in (1) is the average of the individual RMS values of  $n=60$  sectors ( $i$ ) in the noise window (325–430 ms after stimulus onsets). There is no significant effect of mirror-excursion amplitude (0 or 2°) on the RMS-average obtained for the noise window. An estimate of false positive rates was obtained from the distribution of SNR values for the noise window following Hood et al. (2002):

$$\text{SNR}_{ij} = \text{RMS}_{ij}(325 \text{ to } 430 \text{ ms}) / [\sum_i \text{RMS}_{ij}(325 \text{ to } 430 \text{ ms}) / n] - 1 \quad (2)$$

Thus we obtained  $j \times n$  SNR-values ( $j=8$  subjects;  $n=60$  locations for experiment 1 and  $n=64$  locations for experiment 2). An analysis of the distribution of these SNRs showed that SNRs  $\geq 0.5$  are part of the noise distribution with a probability of 10% and SNRs  $\geq 1.0$  with a probability of 1%. An SNR-threshold of 1.0 will entail an exclusion of subjects for some stimulus conditions. To obtain equal sample sizes for most analysis conditions we applied an SNR-threshold of 0.5. As this might possibly lead to an underestimation of the experimental effects, we verified that similar results were also obtained with the more conservative SNR-threshold of 1. In all our quantitative analyses we compared two stimulus conditions (pattern-reversal vs pattern-onset, or 0 vs 2° mirror excursion). Each stimulus location was required to evoke supra-threshold responses in one of the two conditions to enter the analysis (logical OR-operator). Thus a bias of the results to one of these two conditions due to the thresholding procedure will be avoided: e.g. an AND operator would lead to an *exclusion* of stimulus

locations that are suppressed below the SNR-threshold in only one of the two stimulus conditions and, as a consequence, cause an underestimation of the experimental effects.

To assess the effect of mirror-motion on the mfVEPs we calculated the log-ratio of the supra-threshold responses [ $\log(\text{RMS}_{2^\circ \text{ mirrorexcursion}} / \text{RMS}_{0^\circ \text{ mirrorexcursion}})$ ], as defined above. Thus each subject’s response is normalised with respect to the 0° mirror-excursion condition which reduces the effect of the inter-subject variability of the responses. The resulting log-ratios were grouped according to eccentricity or left/right or top/bottom hemifields for averaging. As the stimulus-locations in the uniform checkerboard stimulus (experiments 2) are not aligned on iso-eccentricity ranges, we weighted an individual location’s response according to its contribution to an iso-eccentricity range before averaging the log-ratios; we obtained similar eccentricity dependences of the experimental effects comparing the non-interpolated responses from the central patches and each of the surrounding three rows of patches.

Univariate repeated measures ANOVAs were applied to the logarithmised RMS-ratios to test the dependence of the experimental effects on stimulation mode, eccentricity, and on the interaction of eccentricity and stimulus for its significance.

#### 2.5. Procedure

Recording sessions were conducted in a dimly lit room and lasted around 2–3 h, including preparation and breaks. Overall, four stimulus conditions were tested, i.e. two stimulation modes (pattern-onset/pattern-reversal) and two mirror-amplitudes (0 and 2°). The session started with a counterbalanced succession (a–b–b–a-scheme) of blocks with a mirror excursion amplitude of 0° (‘a’) and 2° (‘b’) for one stimulation mode. To avoid overspill of the effect of 2° mirror excursion into the 0° condition a break of 5 min duration was inserted. The same succession was then repeated for the other stimulation mode. To balance the design across subjects the session started with pattern-reversal stimulation in four subjects and with pattern-onset stimulation in the other four subjects.

### 3. Results

Examples of the responses to pattern-reversal and pattern-onset stimuli with the scaled dartboard layout (i.e. experiment 1) are given in Fig. 2 for a single subject with and without induced retinal image motion. These responses are spatially arranged as a reprojection of the signals to the visual field locations that evoked them to give a qualitative account of the observed experimental effects. The original traces are depicted in A and C, the RMSs for each of these traces are depicted in B and D, where symbol size represents

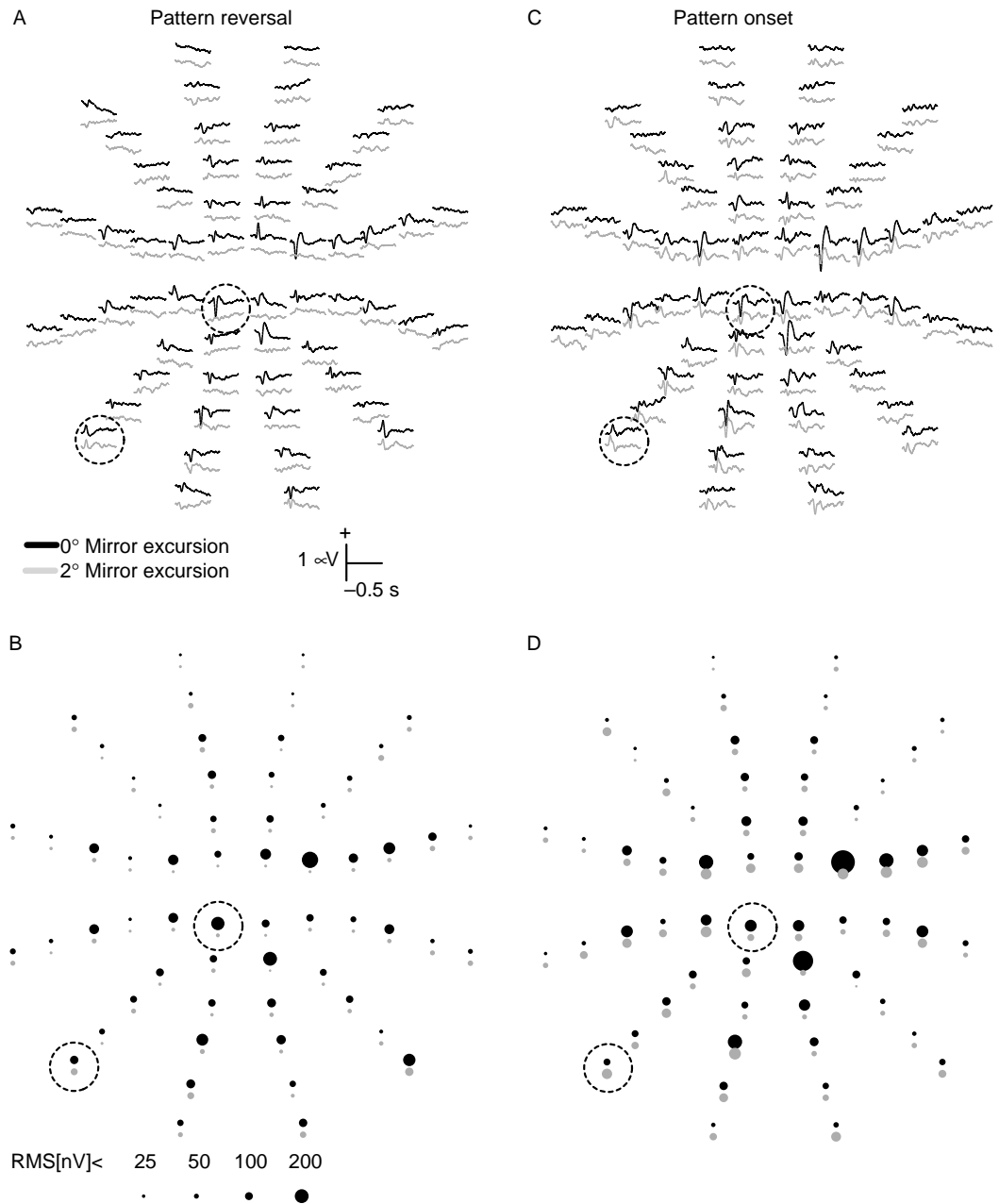


Fig. 2. mfVEP examples for the scaled dartboard stimulus pattern, i.e. experiment 1: mfVEPs to pattern-reversal (A) and pattern-onset (C) and the corresponding RMS-values (B and D) from a single subject without and with a mirror excursion of 2°, in black and grey, respectively (the responses for the two conditions are displaced with respect to each other for clarity). Traces and blobs are arranged according to the spatial layout of the visual field locations that evoked them; note that traces from different eccentricities are arranged in an equidistant manner, while the actual stimulus layout is approximately m-scaled. Typical features of the mfVEP such as the polarity reversal near the horizontal meridian are evident. The dotted circles highlight the effect of the mirror excursions: a strong reduction of pattern-reversal responses in the centre and a weaker reduction in the periphery, while pattern-onset responses are only weakly affected in the centre and even enhanced in the periphery.

RMS magnitude. In addition to the typical features of mfVEP recordings, i.e. the great variability of signal strength and signal shape across the visual field, it is evident that the effect of retinal image motion on mfVEPs depends on eccentricity and stimulation mode (see dotted circles): mfVEPs are markedly reduced in the visual field centre, while peripheral responses are only mildly reduced,

or, as observed for pattern-onset stimulation, even enhanced.

We analysed the above features of the mfVEPs quantitatively for Fig. 4(A–C). In part A we depicted the mean RMS of the pattern-onset response relative to the pattern-reversal response as a function of eccentricity. A ratio smaller than 1.0 indicates greater pattern-onset



responses, while a ratio greater than 1.0 indicates greater pattern-reversal responses. The RMS-ratio depends on eccentricity ( $P < 0.0001$ ). It is evident that pattern-onset responses exceed pattern-reversal responses in the central visual field, while they are smaller in the periphery, which is in agreement with a previous report (Hoffmann et al., 2003a). In part B and C, we depicted the mean RMS of the response with induced retinal image-motion ( $2^\circ$  mirror excursion) relative to that without ( $0^\circ$  mirror excursion) as a function of eccentricity (B) and visual hemifield (C) for both stimulation modes, i.e. pattern-reversal and pattern-onset stimulation. A ratio smaller than 1.0 indicates a response reduction during retinal image motion, while a ratio greater than 1.0 indicates a response increase during retinal image motion. RMS-ratios depend on eccentricity ( $P < 0.0001$ ) and stimulation mode ( $P = 0.001$ ). Pattern-reversal responses are reduced at all stimulus eccentricities, but in an eccentricity-dependent manner, the greatest reduction, by 73%, is observed in the visual field centre. There is also an eccentricity-dependent reduction of the pattern-onset responses, but in contrast to the pattern-reversal responses, they are reduced by only 42% in the visual field centre and even enhanced by 39% in the outmost eccentricity tested. During retinal image motion left hemifield responses were less reduced than right hemifield responses (part C;  $P = 0.017$ ); this left–right asymmetry is likely to be related to the left–right asymmetry of the simulated horizontal nystagmus, which shifts left stimulus patches towards the central retina and right patches towards the peripheral retina. There was no significant top–bottom asymmetry.

In experiment 1 pattern-onset responses from the outmost ring were enhanced. As the outmost ring constitutes the largest patch size, this response enhancement might be related to the size of the stimulus patch used, or to the eccentricity of the stimulus. In the latter case it might even be an edge-artefact, due to an interference of the stimulus with un-stimulated regions neighbouring the outmost ring during induced retinal image motion. Therefore, we conducted experiment 2 with a uniform stimulus comprising  $8 \times 8$  stimulus patches, each spanning  $3.5^\circ \times 3.5^\circ$  (see Fig. 1B). While such a uniform stimulus is suboptimal for conventional mfVEP recordings (Baseler et al., 1994; Whang et al., 2001), it suits the requirements of our control experiment. Examples of the responses recorded in a single subject to pattern-reversal and pattern-onset stimulation during or in the absence of induced retinal image motion are given in Fig. 3. The figure is arranged similarly to Fig. 2 and gives a qualitative account of the experimental effects. As expected, a striking feature is the scarcity of sizable responses. This is a direct consequence of the stimulus layout used: In this stimulus, the central 3 rings, i.e. 24 distinct visual field locations which contribute most to the mfVEP response, of the scaled dartboard-pattern used in experiment 1, collapse, in the absence of any m-scaling,

into only four locations. Apart from this feature, which is a consequence of the use of a uniform checkerboard-pattern for stimulation, it is evident that pattern-reversal responses are reduced during retinal image motion while pattern-onset responses are enhanced.

A quantitative account of the dependence of the mfVEP responses on specific groups of visual field locations is given in Fig. 4(D–F). In part D, we depicted the mean RMS of the pattern-onset response relative to the pattern-reversal response as a function of eccentricity. The RMS-ratios depend significantly on eccentricity ( $P = 0.008$ ); central pattern-reversal responses are greater than pattern-onset responses, while the inverse relationship applies to peripheral responses. This contrasts with the eccentricity dependence reported for experiment 1 and indicates that pattern-reversal and pattern-onset responses depend not only on eccentricity, but also on check- or patch-size. In part E and F, we depicted the mean RMS of the response with induced retinal image-motion relative to the mean RMS without as a function of eccentricity and visual hemifields, respectively. In all three comparisons, pattern-onset response ratios clearly exceed pattern-reversal response ratios ( $P < 0.0001$ ; pattern-onset responses are enhanced by 17% while pattern-reversal responses are reduced by 27%). RMS-ratios depend significantly on eccentricity ( $P = 0.018$ ), but not on the stimulated hemifield.

#### 4. Discussion

Simulated nystagmus influences pattern-reversal and pattern-onset mfVEPs in a differential way. It reduces pattern-reversal responses in an eccentricity-dependent manner with the greatest reduction in the central visual field, while pattern-onset responses are reduced by less or even enhanced, depending on stimulus eccentricity and the specific stimulus layout used.

##### 4.1. Origin of the differential reduction of pattern-reversal and pattern-onset mfVEPs

Our finding that simulated nystagmus reduces pattern-reversal mfVEPs much more than pattern-onset mfVEPs clearly resembles previous cVEP studies (Hoffmann et al., 2004; Saunders et al., 1998), which demonstrated that sizable pattern-onset cVEPs can be obtained in the presence of genuine or simulated nystagmus, while pattern-reversal cVEPs are severely degraded. Which mechanism mediates this differential effect of retinal image motion? Based on cVEP-experiments, it has been argued that retinal image motion degrades pattern-reversal responses due to adaptation to the moving pattern (Bach and Ullrich, 1994; Hoffmann et al., 1999, 2004). This hypothesis is based on the fact that the pattern is visible and therefore a potential adaptor for 100% of the stimulation time during pattern-reversal stimulation and only for down to 12% during

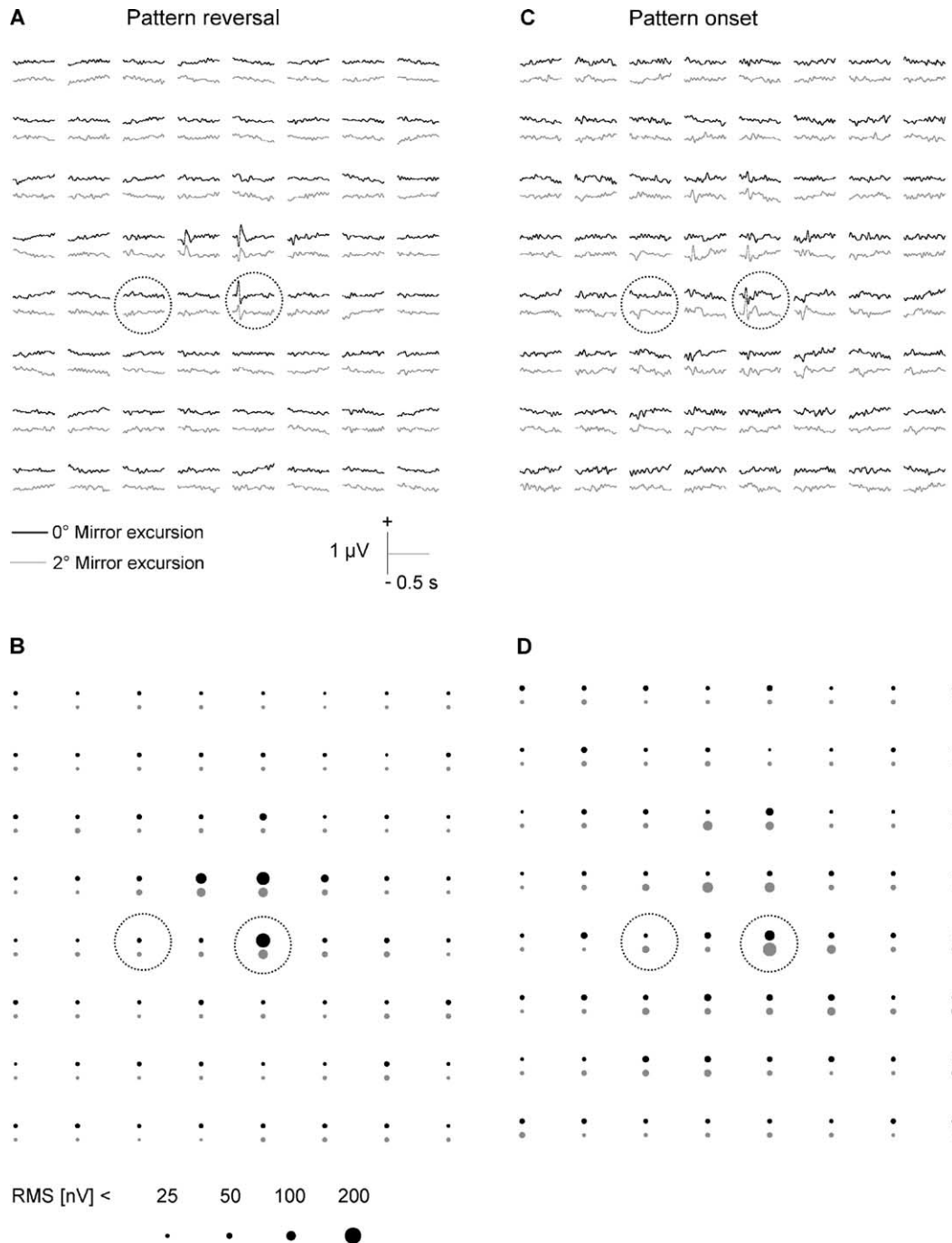


Fig. 3. mfVEP examples for the uniform checkerboard stimulus pattern, i.e. experiment 2: mfVEPs to pattern-reversal (A) and pattern-onset (C) and the corresponding RMS-values (B and D) without and with a mirror excursion of 2°, in black and grey, respectively (the responses for the two conditions are displaced with respect to each other for clarity). Traces and blobs are arranged according to the spatial layout of the visual field locations that evoked them. Typical features of the pattern-reversal mfVEP such as the polarity reversal near the horizontal meridian are evident, although responses are scarce due to the lack of scaling in the stimulus pattern. The dotted circles highlight the effect of the mirror excursions: pattern-reversal responses are strongly reduced, while pattern-onset responses are enhanced.

pattern-onset stimulation. In the present mfVEP study, these values are 100 and 50%, respectively, opening the possibility that also for mfVEPs motion adaptation might be the mechanism by which the differential effect of retinal image motion on pattern-reversal and pattern-onset VEPs is mediated.

#### 4.2. Eccentricity dependence of the effect of simulated nystagmus on mfVEPs

The effect of retinal image motion on pattern-reversal mfVEPs depends on eccentricity for both scaled and un-scaled stimuli, although the dependence is much more

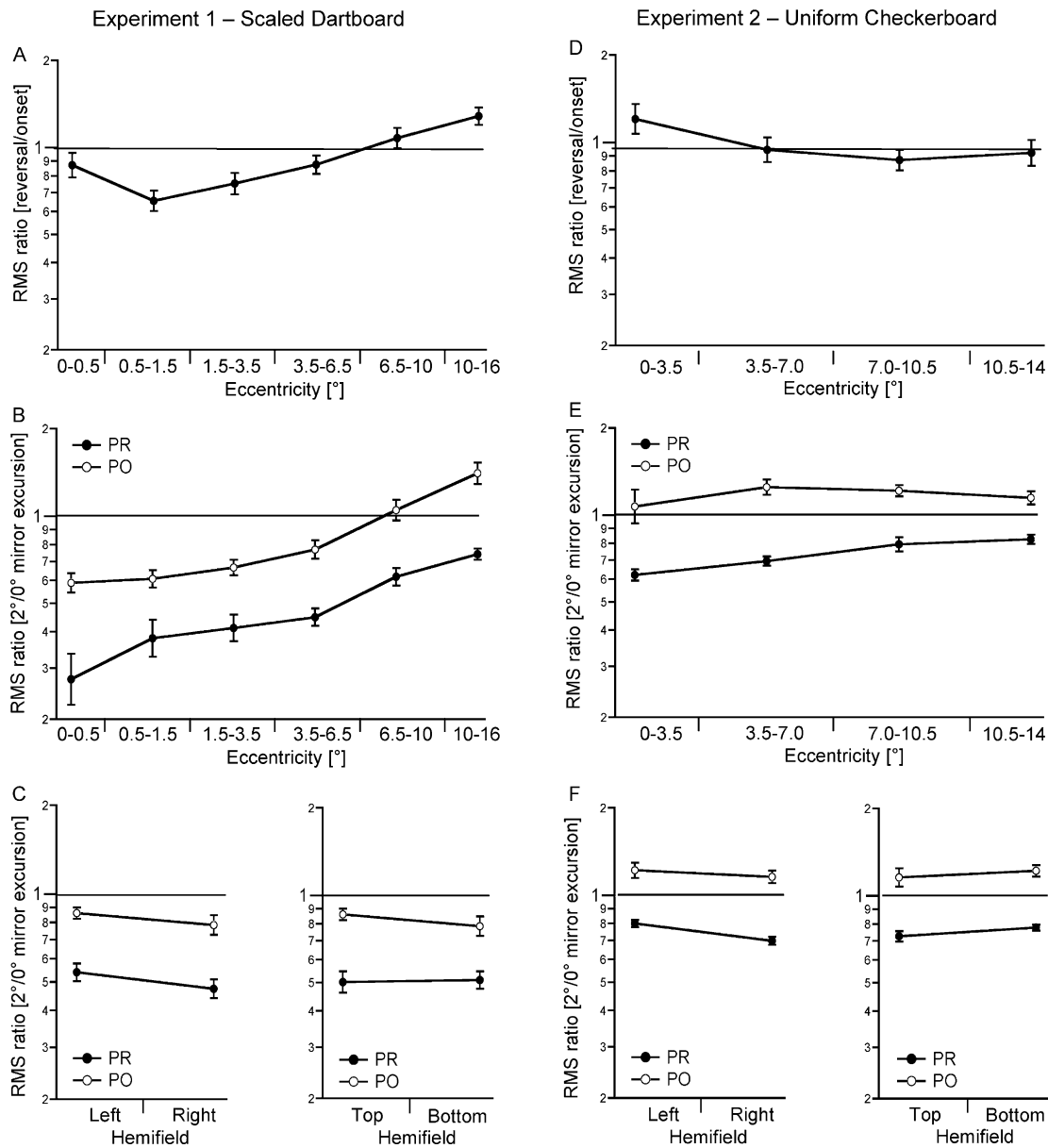


Fig. 4. Mean RMS ratios as a function of eccentricity and visual hemifield. (A–C) results for the scaled dartboard stimulus pattern, i.e. experiment 1 (mean  $\pm$  SEM;  $n=8$  except the first eccentricity:  $n=6$ ): (A) RMS ratios of pattern-reversal (PR) and pattern-onset responses (PO). In the central visual field pattern-onset responses exceed pattern-reversal responses, while they are smaller in the periphery. (B) RMS ratios of responses during 2° mirror excursion and no mirror excursion for pattern-reversal (filled symbols) and pattern-onset (open symbols) as a function of eccentricity. Central pattern-reversal responses are more strongly reduced than peripheral. Pattern-onset responses are weakly reduced and even enhanced in the periphery. (C) Same as for (B), but as a function of visual hemifields. There is a slight, but significant left–right asymmetry. (D–F) results for uniform checkerboard stimulus pattern, i.e. experiment 2 (mean  $\pm$  SEM;  $n=8$ ): (D) RMS-ratios of pattern-reversal (PR) and pattern-onset responses (PO). The eccentricity dependence of the RMS-ratios reaches significance. (E) RMS ratios of responses without mirror excursion and during 2° mirror excursion for pattern-reversal (filled symbols) and pattern-onset (open symbols) as a function of eccentricity. Pattern-reversal responses are reduced, while pattern-onset responses are enhanced by the mirror excursions. (F) Same as for (E), but as a function of hemifields. There is no significant dependence of the ratios on the hemifields.

pronounced for the scaled patterns. For pattern-onset mfVEPs this eccentricity dependence is only evident for a scaled stimulus pattern. Two previously reported findings might help to understand this eccentricity dependence: (1) A side-effect of simulated and genuine nystagmus is the reduction of visual acuity due to motion blur of the retinal image (Bedell and Loshin, 1991; Chung and Bedell, 1997). (2) Reduced visual acuity degrades mfVEPs to a scaled

dartboard pattern preferentially in the central visual field (Pieh et al., 2005). Taken together, the reduction of visual acuity by simulated nystagmus is likely to mediate the pronounced reduction of mfVEPs obtained for the centre of a scaled dartboard pattern. Furthermore, this mechanism would also explain why, for a uniform checkerboard stimulus with a large check-size (experiment 2), the eccentricity dependent reduction is smaller or even absent.



#### 4.3. Enhancement of pattern-onset mfVEPs by retinal image displacement—a perspective for a novel stimulus?

The enhancement of pattern-onset responses by retinal image displacement was an unexpected and serendipitous finding. While this response enhancement was restricted to the outmost ring for the scaled-dartboard experiment, it was also evident for more central locations in the uniform-checkerboard experiment and is therefore not simply due to interference-effects at the stimulus border. As previously reported, pattern-onset mfVEP responses are enhanced when stimulation rate is reduced (James, 2003). Remarkably, retinal image displacement will also reduce the effective stimulation rate of an individual neuron, as different neuronal populations are likely to be activated for different stimulus positions. As a consequence, pattern-onset mfVEPs recorded at high stimulation rates might possibly be enhanced by the displacement of a stimulus patch's pattern in between pattern-onsets.

#### 4.4. mfVEPs in patients with nystagmus

The present study indicates that mfVEPs might be obtained in patients with moderate oculomotor-instabilities using a uniform checkerboard-pattern driven at pattern-onset mode. Such a stimulus does not allow one to sample the central visual field at a high spatial resolution. It should be noted, however, that the fixation instabilities of the patients already reduce the resolution at which the visual field can be sampled. As a consequence, a dense sampling of the central visual field would not be of additional benefit in these patients. A different class of problems might arise from a possible interference of the m-sequences of distinct stimulus patches with each other. In principle, an interference of the m-sequences is avoided in the multifocal approach by the use of orthogonal m-sequences, retinal image displacement, however, might affect this orthogonality: due to retinal image displacement, a stimulus patch driven by a particular m-sequence will activate different retinal regions and consequently different cortical generators during different phases of retinal image displacement. As these different cortical generators might, due to cortical convolution, have different orientations relative to a particular derivation, some of them might fail to project onto this derivation and thus fail to generate a signal at this derivation. As a consequence, a particular derivation might only 'see' part of the entire m-sequence, which might affect the orthogonality of these m-sequences. The significance of this problem needs to be addressed in further research.

We report that pattern-onset responses are less reduced than pattern-reversal responses or even enhanced by induced retinal image slip. While our findings suggest stimulus conditions for mfVEP-recordings in patients with fixation instabilities, they also indicate how pattern-onset responses might be boosted in subjects without fixation problems.

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