Pattern Onset ERGs and VEPs Produced by Patterns Arising From Light Increment and Decrement

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PURPOSE. Our aim was to elaborate how on and off signals contribute to pattern ERGs and pattern visual evoked potentials (VEPs) by using pedestal patterns arising from incremental and decremental onset stimulation.

METHODS. Pattern onset/offset ERGs and VEPs were produced by black and white checks of $60'$ side length and 88% spatial contrast appearing in a $16°$ field for 200 ms from white (110 cd/m^2), black (7 cd/m^2), and gray (48 cd/m^2) backgrounds and disappeared for 1000 ms. Twenty healthy subjects participated in the study (median age 19.5, range, 5–31 years), 10 of whom also underwent pattern onset/offset ERG recordings to the same stimuli (median age 25.7, range, 22–31 years). VEPs were recorded from an occipital array referred to Fz. Pattern electroretinograms (PERGs) were recorded from "Dawson-Trick-Litzkow" (DTL) plus corneal electrodes referred to ipsilateral outer canthi.

RESULTS. There was high correlation within subjects of the VEP waveform produced by patterns arising from light increment and decrement (group mean correlation coefficient of PVEPs to check appearance from black versus white: 87%). An average of increment and decrement PERGs simulated the onset PERG from a gray background. This waveform is akin to standard International Society for Clinical Electrophysiology of Vision (ISCEV) clinical PERGs to reversing checks.

CONCLUSIONS. In healthy individuals, the early components of the pattern onset/offset VEP waveforms are comparable to light increment and decrement pedestal stimulation. Pattern onset/offset ERGs to pedestal stimulation may be used to probe simultaneous recording of ERGs with VEPs in order to obtain an assessment of retinal ganglion cell and optic pathway function in patients with less stable fixation.

Keywords: ON-pathway, VEP, PERG, congenital nystagmus, OFF-pathway

ON- and OFF-pathways in the visual system convey the perceptions of light increment and decrement to the visual cortex.[1] In primates, a pharmacologic blockade of the ON-bipolar pathway using 2-amino-4-phosphonobutyric acid (APB) results in impairment of light increment perception, as well as loss of contrast sensitivity.[2] Patients with selective ON-pathway dysfunction are identified by flash electroretinograms (ERGs) that have reduced b-waves, so-called electronegative ERGs. This ERG phenotype localizes dysfunction to the synapse between photoreceptors and depolarizing bipolar cells and is a characteristic of the complete type of congenital stationary night blindness (cCSNB or CSNB1). Patients with CSNB1 often show visual problems in dim light conditions,[3–6] but the effects of this retinal dysfunction on subsequent neuronal pathways and cortical vision is not well understood at present.

In clinical electrophysiological practice the visual evoked potential (VEP) and the pattern electroretinogram (PERG) are used to assess visual pathway integrity and retinal ganglion cell function, respectively. Both responses, in accord with the International Society for Clinical Electrophysiology of Vision (ISCEV) standard recommendation, can be produced by phase reversing checkerboard stimuli made up of equal numbers of black and white checks.[7,8] This makes it feasible to assess retinal and optic nerve pathway function simultaneously in the same session.

Nystagmus is frequently seen in patients with a dysfunctional ON-pathway, which can make the electrophysiological recording to pattern reversal stimuli challenging. Although a pattern reversal VEP with normal time to peak can be recorded even in the presence of nystagmus,[9,10] the recording of a PERG—where good image quality and contrast is crucial to obtain a response[8]—can be difficult and results variable.[11]

In such cases, pattern onset stimulation can give insight into visual pathway function.[12,13] Here, we explore the potential of incremental and decremental "pedestal" pattern onset stimulation[14] with the aim of investigating and functionally distinguishing ON- and OFF-pathway contributions to ganglion cell and optic pathway function in healthy volunteers. These tests may present a viable electrodiagnostic alternative in patients with ON-pathway dysfunction who also have nystagmus.

METHODS

Participants

Pattern onset VEP responses were recorded from 20 healthy subjects (median age 19.5 years; range 5–31 years), of whom 10
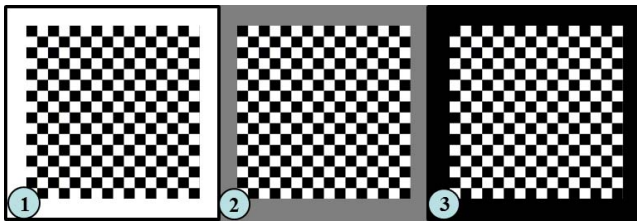
FIGURE 1. Overview of the stimuli used for the pedestal pattern onset VEPs and ERGs. Numbers 1 to 3 illustrate the different stimuli displaying a checkerboard of 88% Michelson spatial contrast appearing from three different backgrounds, with (1) presenting an overall light decrement upon appearance of the checkerboard and (3) an overall light increment; (2) shows the equivalent of a pattern onset VEP stimulus used in clinical practice with no luminance change during stimulation.

were under 18 years of age (median age 10.5 years; range 5–17 years) and 10 were over 18 years of age (median age 27 years; range 22–31 years). The 10 adult subjects also consented to additional PERG recordings (visual acuity range with both eyes viewing: −0.275 to +0.15 logMAR). Onset PERGs were recorded separately from VEPs. For the recordings subjects were refracted as needed for best corrected vision outcome. The research followed the tenets of the Declaration of Helsinki. Informed consent was obtained from the subjects after explanation of the nature and possible consequences of the study. The research was approved by the Research Ethics Committee, NRES Committee London–South East (REC number 14/LO/2136).

Electrode Placement

Pattern onset VEPs were recorded from an occipital array referred to Fz. An electroencephalogram (EEG) was recorded from the scalp overlaying the visual cortex (active electrode positions: O2, Oz, O1, P3, Pz, P4, inion, reference: Fz, ground: T3) following the international 10-20 EEG electrode placement system. Pattern onset ERGs were recorded from "Dawson-Trick-Litzkow" (DTL) plus corneal electrodes (Diagnosys LLC, Cambridge, UK) referred to outer canthi. Responses were recorded with both eyes viewing.

Specifications

Pattern onset VEPs and pattern ERGs were recorded as continuous electroencephalography files using Neuroscan 4.2 software (Compumedics Ltd., Victoria, Australia). Amplifiers were set to an A/D rate of 1000 and had a band pass of 0.5 to 100 Hz. For stimulus generation, the Stim2 software was used (Compumedics Ltd.). The stimulus generation software sent out a trigger every time the stimulus was displayed to allow subsequent offline analysis of the continuous EEG file via epoching and averaging. One epoch was defined as the time range from 15 ms before stimulus/trigger until 400 ms after stimulus/trigger in order to capture all relevant components of VEP waveforms. An online artifact rejection was enabled for all responses outside of ±150-μV amplitude; responses with amplitudes falling outside of this range were rejected automatically. For each subject 150 accepted sweeps (2 × 75) were recorded for each VEP testing condition. PERG responses were averaged over 2 × 200 sweeps per condition in order to show repeatability. In order to distinguish the small-amplitude signals from noise, the mean noise level encountered in all subjects was retrieved by measuring the waveforms' mean deflection from zero over a period of 10 ms before stimulus. Subsequently, the 95% confidence interval (CI) of the

noise was calculated. For the VEP recordings, the mean noise level was 0.93 μV with a 95% CI ranging from 0.55 to 1.29 μV; however, to obtain more robust values, we doubled the cutoff limit in order to achieve a supra-threshold level. The VEP components therefore needed to have an amplitude of at least 2.58 μV. For the PERG recordings, the mean noise level was 0.22 μV with a 95% CI ranging from 0.16 to 0.29 μV. At supra-threshold level, the PERG components needed to have an amplitude of at least 0.58 μV. Investigating the PERG offset response can be problematic due to the potential of blink artifacts at the end of the inter-stimulus-interval (ISI). Choosing a poststimulus time window for the expected occurrence of the offset response is advised as highlighted in Figure 5. Here, we were looking for a deflection from zero between 80 and 120 ms after stimulus offset.

Stimuli

Electrophysiological stimuli were black and white checks of side length 60' and 88% Michelson spatial contrast appearing in a 16° square stimulus field viewed at 1 m (within a bright 110 cd/m² surround of 87° × 62°). Stimuli were presented on a plasma display panel. Each stimulus was presented with one of three backgrounds—white background (mean luminance 110 cd/m²), gray background (mean luminance 48 cd/m²), black background (mean luminance 7 cd/m²)—for 1000 ms, after which a checkerboard stimulus of the same size covered the same area for 200 ms. Representations of the pattern stimuli used in this study are displayed in Figure 1. These three stimuli were used to elicit pattern onset VEPs and ERGs.

RESULTS

VEP Results

In order to functionally distinguish ON- and OFF-pathways we recorded pattern onset VEPs to patterned stimuli arising from a
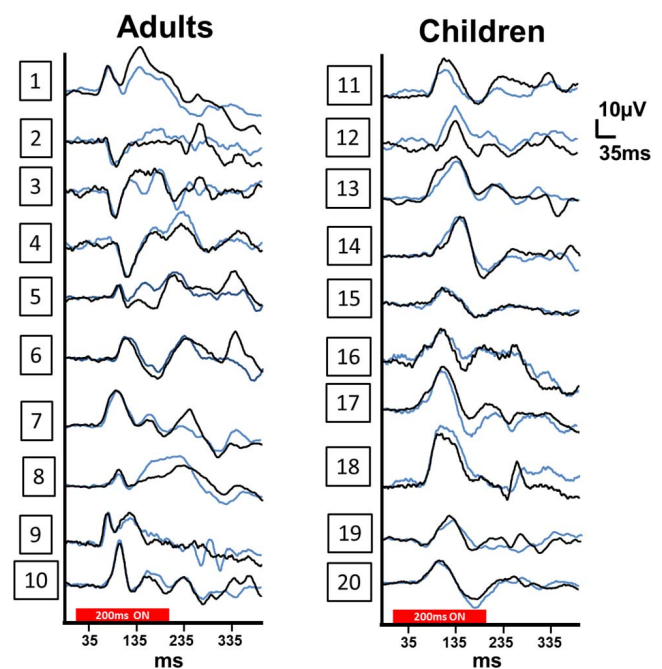

FIGURE 2. Pedestal pattern onset VEPs elicited with light increment (*blue*) and light decrement (*black*) stimulation overlaid for comparison. Each trace is an average of 150 sweeps recorded from Pz. Stimulus duration is displayed in *red*. Subjects arrayed in descending age order.
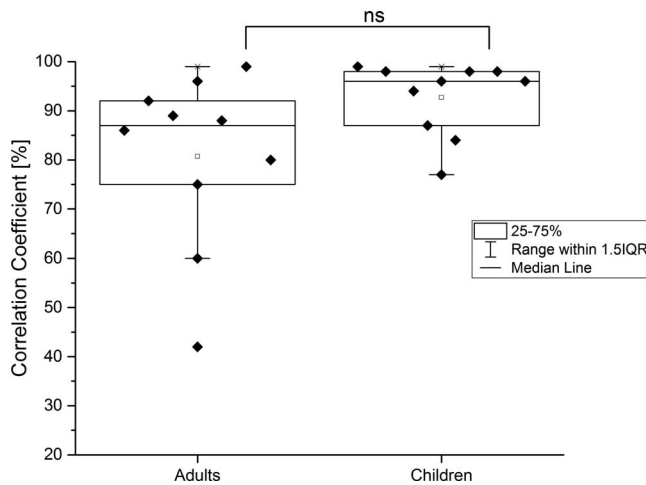
FIGURE 3. Comparison of the correlation coefficients obtained for each group from light increment and decrement VEP recordings. *Black diamonds* represent the individual subjects. *Boxes* give max and min (x), mean (*square*), and median (*border inside the boxes*), as well as 75% and 25% (*margins of the boxes*) percentiles. The children group displays an overall higher mean and median CC between the two conditions, as well as a narrower range of values. However, statistical analysis did not find a significant difference between the two groups (2-sample *t*-test: $P = 0.063$).

FIGURE 5. Pedestal pattern onset ERGs of adult subjects elicited with light increment (*blue*) and light decrement (*black*) stimulation are overlaid for comparison. Each trace is an average of 2×200 sweeps. Recordings were binocular; however, left eye is always displayed. No difference between right and left eye waveforms was observed. Stimulus duration is displayed in *red*. The time window used for investigation of the offset response is highlighted in *gray*.

black background (light increment) and a white background (light decrement), respectively. Reliable pattern onset VEP waveforms were recorded from all subjects to all three background conditions. Although the waveforms of the pattern onset VEPs varied across subjects and with age, within a healthy individual there was good concordance between waveforms produced by patterns appearing due to light increment and decrement (Fig. 2). In view of this variability, we chose to analyze the waveform shape and timing by calculating the correlation coefficient (CC) for each subject, rather than carrying out a simple component analysis. For this, we compared the waveform behavior and shape over a time period of 400 ms by comparing two corresponding points from the light increment and decrement conditions per millisecond.
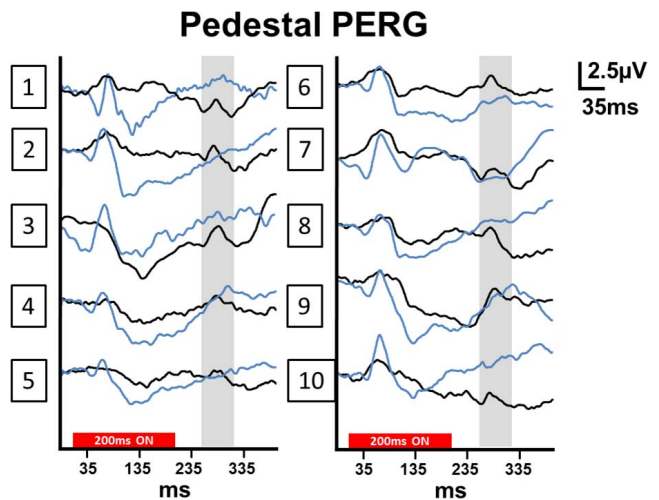
Hence, the similarity of both responses is calculated with a resolution of 400 points (1 point/ms). Resulting from this, the overall group mean CC was 87% with the smallest correlation within one subject being 42% and the highest 99% (Table).

Upon exploring the results empirically it seemed that in children the CC was higher than in adults; however, upon statistical analysis, this was not significant (2-sample *t*-test: $P = 0.063$; Fig. 3). Overall, the waveform shapes obtained from children were less variable than those from adults, with all of them showing a big positive first peak followed by a negativity. The waveform of the pattern onset VEP matures and becomes more complex with age and continues to differentiate into the three clear components, C1:C2:C3, by around 45 years.[15] Some young adult subjects showed similar-looking waveforms to children; others also displayed more complex responses. The
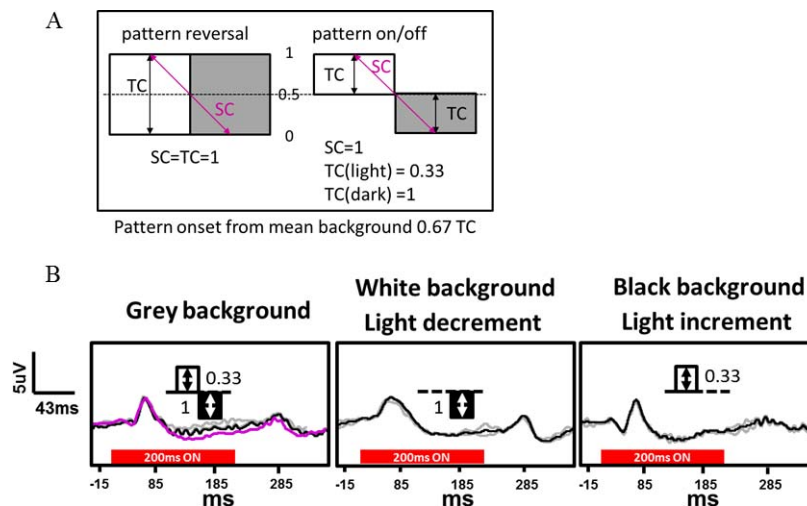

FIGURE 4. **(A)** A Reversal stimulus has equal spatial contrast (SC) and temporal contrast (TC), but a pedestal onset stimulus differs for light ON and light OFF and has a lower space-averaged temporal contrast of 67%.[22] **(B)** Representative pattern onset ERG traces of one subject for all three stimulations. *Gray traces* represent 200 averaged sweeps; *black traces* are averages of these. Offset PERGs are enhanced by light decrement. Onset PERGs have prominent N35 to light increment. An average of pedestal PERGs simulates the onset PERG from gray background (*purple overlay, column 1*).

Table. Correlation Coefficients of Pedestal Pattern Onset VEP Waveforms Across Subjects

Subject	Correlation Coefficient, %	95% CI Lower Limit, %	95% CI Upper Limit, %	Subject	Correlation Coefficient, %	95% CI Lower Limit, %	95% CI Upper Limit, %
1	75	66	82	11	96	95	97
2	96	95	98	12	94	91	96
3	60	47	70	13	98	97	99
4	88	83	91	14	98	97	99
5	42	26	56	15	84	78	87
6	89	85	93	16	87	82	91
7	92	88	94	17	98	97	99
8	99	98	99	18	99	98	99
9	80	73	86	19	77	69	84
10	86	80	90	20	96	93	97
Mean CC > 18 y		80.7 ± 17.6		Mean CC < 18 y		92.7 ± 7.5	
Total mean CC		87		Total MIN CC, %	42	Total MAX CC, %	99

Values represent the percentage of correlation for waveforms obtained to light increment and decrement, as well as the 95% confidence interval. The closer this value is to 100, the more similar are the two waveforms. Mean CC is always given as percentage. Total mean CC is given with total minimum (MIN) and maximum (MAX) values, and mean CC of groups older and younger than 18 years is given with standard deviation (SD).

early peaks within 65 to 145 ms were the most similar when produced by light increment and decrement. This was supported by the finding that a higher group CC (90%) was achieved when analyzing only a duration of 200 ms from stimulus onset focusing on the timing of the first positive peak.

PERG Results

Although pattern onset stimulation from a gray background displays less temporal contrast than reversal stimulation,[16] we were able to produce consistent onset PERGs in our cohort. These waveforms were akin to those obtained from clinical reversal stimulation when stimulation occurred from a gray background (Fig. 4B, first part of figure). The standard ISCEV PERG waveform is identified by three main components: N35, P50, and N95. When patterns appeared from a black background (light increment), a pronounced negativity with a timing matching the N35 could be observed immediately before the main positive peak (P50). Upon light decrement stimulation (pattern appearing from a white background), this negativity was not evident in any of the subjects, but a second prominent positive peak emerged at approximately 250 ms post stimulus, which most likely represents the stimulus offset response (Fig. 4B). Further, when averaging light increment and decrement responses together, the resulting waveform is almost identical to the one obtained from clinical pattern onset stimulation to a gray background (Fig. 4B, purple trace). An overview of all traces is given in Figure 5.

The amplitudes of the N35, P50, and N95 components were statistically different between the light increment, decrement, as well as gray background conditions with the light increment conditions giving consistently the biggest and best-defined responses (Fig. 6A). Responses elicited from light decrement stimulation were consistently smallest for these components, with the responses elicited to the gray background condition being of intermediate amplitude. This picture was reversed when looking at the offset response, where the light decrement condition provoked the biggest responses and the light increment condition the smallest (1-way ANOVA with repeated measures and post hoc Bonferroni means comparison: P50: increment > decrement $P = 0.001$, increment > gray $P = 0.0055$; N95: increment > decrement $P < 0.001$, increment > gray $P < 0.001$; offset: decrement > increment $P = 0.0108$, offset decrement > gray $P = 0.0418$). When times to peak were compared across conditions and components, no statistically significant difference was found (Fig. 6B).
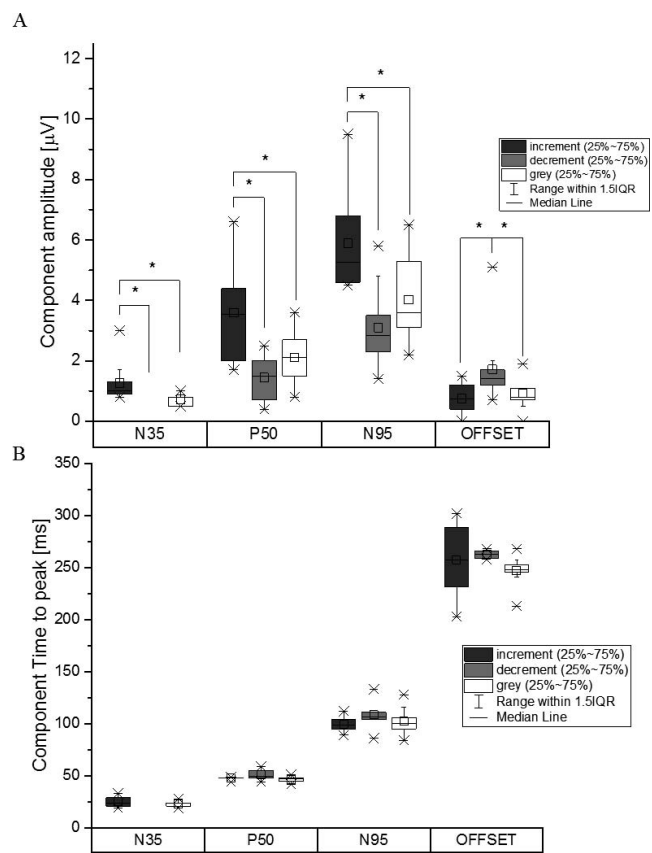
A

B

FIGURE 6. (A) P50 amplitude increased significantly in the light increment condition. ANOVA with repeated measures and post hoc Bonferroni means comparison: P50: increment > decrement $P < 0.001$, increment > gray $P = 0.006$; N95: increment > decrement $P < 0.001$, increment > gray $P < 0.001$; OFFSET: decrement > increment $P = 0.011$, offset decrement > gray $P = 0.042$. (B) P50 time to peak does not differ significantly across testing conditions. (C) Amplitudes of the offset responses to all three stimulation conditions were not significantly different. *Boxes* give max and min (*x*), mean (*square*), and median (*border inside the boxes*), as well as 75% and 25% (*margins of the boxes*) percentiles.
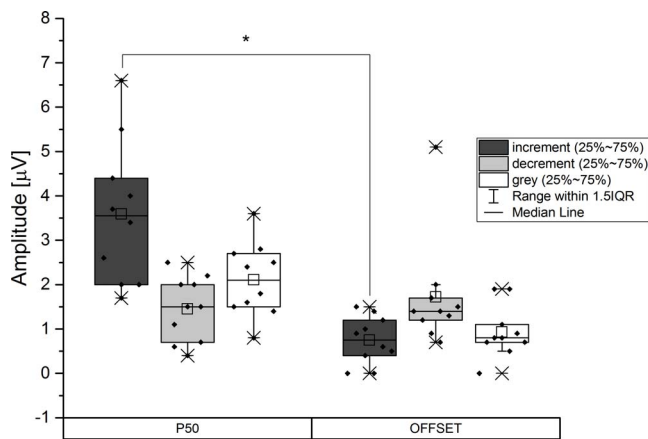
FIGURE 7. The P50 and offset amplitudes of corresponding testing conditions were similar for gray and white backgrounds (light decrement). P50 amplitude to light incremental stimulation was significantly higher in the cohort compared to the corresponding offset response (ANOVA with repeated measures and post hoc Bonferroni means comparison: *P* < 0.001). *Boxes* give max and min (*x*), mean (*square*), and median (*border inside the boxes*), as well as 75% and 25% (*margins of the boxes*) percentiles.

Upon closer component analysis of the onset PERG waveforms obtained in our study group, we found that onset response (P50) amplitudes to 60′ checks across all conditions were constantly bigger than offset response amplitudes. Similar results were previously reported by Arden and Vaegan and others.[17–19] This difference was not found to be significant when patterns arose from gray or white backgrounds (light decrement); however, in response to a light increment, onset amplitudes were significantly higher than the corresponding offset response (*P* < 0.001, Fig. 7).

DISCUSSION

In this study we have applied a set of electrophysiological tests assessing retinal ganglion cell, as well as visual pathway function, separately in the ON- and OFF-pathways of the visual system. This was achieved by utilizing conventional pattern onset stimulation and introducing a pedestal light increment and decrement component by presenting checkerboards arising from a black or white background, respectively. We were able to show that pattern onset VEPs are similar to incremental and decremental pedestal stimulation in healthy observers. Although there was waveform variation across the subject cohort, a good concordance within individual subjects was observed. Generally, the first positive peak seemed to be the most robust component when produced by light increment and decrement. These results suggest local spatial contrast changes rather than luminance changes (temporal contrast) to be the driver of these responses. This agrees with earlier work by Spekreijse, Estevez, and Van der Tweel,[20] as well as Riemslag and colleagues,[21] who found that cortical responses show a spatial contrast dependence. If it was temporal contrast, we may expect a bigger difference between incremental and decremental responses according to the inherent asymmetry in temporal contrast magnitude proposed by Drasdo and colleagues[22] (Fig. 4A).

In addition to VEPs, pattern onset ERGs were recorded to the same stimuli in order to capture inner retinal contributions of ON- and OFF-pathways. The summation of the increment and decrement PERGs showed great similarity to the waveforms obtained from a conventional clinical pattern reversal

ERG with the main components being observed. Previous research established that there is no peak latency variation in the onset PERG with changing contrast.[23] We show here that the same is true when PERGs are elicited by patterns arising from light increments and decrements. In contrast, a marked difference in peak amplitude between onset PERGs produced by light increment and decrement was observed in this study. Not only were N35, P50, and N95 components significantly larger during light incremental stimulation, but the occurrence of an N35 was not observed in light decremental PERGs at all. A wealth of studies highlight an asymmetry in the processing and perception of darks and lights by the visual system. Initiated by Galilei's[24] irradiation illusion highlighting a higher visual spatial resolution for dark stimuli compared to light stimuli, this phenomenon was subsequently supported by more recent findings that OFF-center afferents dominate the cortical representation of central vision,[25] and that cortical neurons are more strongly driven by darks than by lights at low spatial frequencies.[26] These studies reveal a fundamental difference between ON-and OFF-pathway representation and processing in the cortex. Our results would agree with a larger retinal signal gain exhibited in the ON-pathway compared with a subsequently larger cortical signal gain in the OFF-pathway, as the subsequent cortical VEP waveforms to incremental and decremental stimulation were highly similar. At the retinal level, PERGs were bigger and better defined to light incremental stimulation, hinting at a potential advantage of the ON-system at this stage.

Pharmacologic studies have suggested that ON- and OFF-pathways contribute equally to the conventional pattern reversal ERG.[27] Interestingly, we found the pattern ERG offset response in our cohort to be of smaller amplitude than the pattern onset response. This was significant in the light increment condition. The check size used in this study (60′) might be the cause of this, as the amplitude of the offset response exhibits low-pass spatial tuning with larger amplitudes encountered using big check sizes.[18,19,23] Another possibility is that the offset response is driven more by temporal contrast than the onset response at this spatial frequency, resulting in different-sized components.[28] Furthermore, in this study, a substantial offset response was elicited only if the temporal contrast of the stimulus was higher than 33%, that is, in the light increment condition and when stimuli were appearing from a gray background.

In conclusion, our results show that pedestal pattern onset stimulation can be useful to assess ganglion cell as well as visual pathway integrity selectively in ON- and OFF-pathways. VEPs recorded from healthy volunteers show a high correlation when waveforms elicited to light incremental and decremental stimulation are compared. Pattern onset ERGs are of comparable morphology to conventional clinical pattern reversal ERG waveforms, displaying all major components. Pattern onset ERGs may be recorded simultaneously with onset VEPs.

These results suggest that these stimuli offer an effective means of investigating a dysfunctional ON-pathway and distinguishing ON and OFF signals from optic nerve and striate cortex. In particular, they can provide an alternative stimulus for assessing visual function in patients with ON-pathway dysfunction who can also have nystagmus.

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