Minor effect of blue-light filtering on multifocal electroretinograms

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PURPOSE: To assess the impact of blue-light filtering on retinal processing to evaluate potential side effects of these filters on visual function at the neural level.

SETTING: Department of Ophthalmology, Otto-von-Guericke-University Magdeburg, Magdeburg, Germany.

DESIGN: Cohort study.

METHODS: Multifocal electroretinograms (ERGs) were recorded monocularly after pupil dilation in pseudophakic patients with a colorless intraocular lens (IOL) under 2 conditions: (1) stimulus perception through a yellow-tinted filter with the filter characteristics of the AF-1 YA-60BB IOL (blue-light filter) and (2) stimulus perception through a neutral filter that homogeneously attenuates the effective stimulus intensity like the blue-light filter independent of the wavelength. First-order kernel multifocal ERGs were extracted at 61 visual field locations and averaged for 5 stimulus eccentricities. Amplitudes and implicit times were determined for the multifocal ERG components N1 (first negative deflection), N2 (second negative deflection), and P1 (first positive deflection).

RESULTS: The study evaluated 20 patients. Typical multifocal ERGs were obtained for both conditions at all eccentricities. There were no significant differences in amplitudes or implicit times between the 2 conditions except for a slight P1 amplitude enhancement (6.9%) with the blue-light filter at an intermediate eccentricity ($P = .003$).

CONCLUSIONS: The bipolar cell-dominated multifocal ERG was largely unaffected by short-term effects of blue-light filtering. The induced change in the spectral composition of the stimulus did not significantly alter the activity at the input stage of the visual system, specifically the retinal network comprising photoreceptors, horizontal cells, and bipolar cells.

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Replacing the crystalline lens with a colorless intraocular lens (IOL) in cataract surgery increases the amount of radiation that reaches the retina. Intraocular lens implantation would therefore increase the risk for photic retinopathy. To reduce this risk, many cataract surgeons implant IOLs that eliminate ultraviolet radiation, and IOLs that eliminate a broader range in the short-wavelength spectrum might further decrease the risk.[1] The latter IOLs are commonly referred to as blue-light filtering, and their use might protect the retina, in particular the macula.[2–4]

However, blue-light filtering might affect visual processing. Accumulating evidence suggests that performance in subjective visual tests, specifically contrast sensitivity and color perception, is slightly affected or not affected by blue-light filtering.[5–13] However, because these psychophysical studies tap the system at its output stage, the effects of filters on the underlying neural activity might be obscured by compensatory mechanisms along the processing chain in the visual pathways. It would, therefore, be beneficial to clarify whether neural signals close to the input stage are affected by filter-related changes in the spectral composition of the visual stimuli. To our knowledge, no published study has assessed the effect of blue-light filtering on visual processing in humans using objective

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techniques to directly probe the neural substrate. Furthermore, previous psychophysical studies do not take into account that the effects of filtering might vary across the retina (eg, with retinal eccentricity) because of the variation in spectral sensitivities across the retina.

The ideal tool for a spatially resolved assessment of the functional integrity of the visual system close to the input level is the multifocal electroretinogram (ERG).[14] With the multifocal ERG, responses are derived simultaneously from many retinal locations in a short interval. Thus, topographic maps of retinal function can be obtained within a few minutes of recording time. Multifocal ERGs are dominated by the activity of retinal bipolar cells,[15] and they are expected to provide insight into the neural activity associated with a retinal network comprising photoreceptors, horizontal cells, and bipolar cells.

The aim of the present study was to isolate the effect of blue-light filtering on retinal function. The effect was assessed in a spatially resolved manner using multifocal ERGs. We evaluated eyes with a colorless IOL using a paradigm that allowed intraindividual comparisons to increase the sensitivity of the approach. For this purpose, multifocal ERGs were recorded for stimuli viewed through a blue-light filter and through an equivalent neutral filter.

PATIENTS AND METHODS

Multifocal ERG recordings were performed monocularly in pseudophakic patients at least 6 months after cataract surgery. All IOLs implanted during surgery were colorless and had a spherical design. The procedures followed the Tenets of the Declaration of Helsinki,[16] and the protocol was approved by the Ethics Committee, University of Magdeburg, Germany. All patients gave informed written consent before the study.

Exclusion criteria were a history of ocular trauma, retinal surgery, intraocular infection, dilated pupil diameter 6.5 mm or smaller, anterior or posterior synechiae, clinically significant macular edema, age-related macular degeneration, epiretinal gliosis, diabetic retinopathy, corneal opacity, manifest glaucoma, a corrected distance Snellen visual acuity[17] worse than 20/50, and unstable fixation. Patients with strabismus were also excluded.

Filters

To isolate the effect of wavelength-specific filtering on the multifocal ERG, a filter with the absorption characteristics of the AF-1 YA-60BB IOL (Hoya Surgical Optics GmbH) was used. Because the filter mostly eliminates the short-wavelength range, it is referred to here as a blue-light filter. In addition to suppressing the short-wavelength range, the filter reduces the transmission of the entire visible spectrum (Figure 1). Thus, in addition to the changes in the spectral composition of the stimulus, the stimulus luminance is reduced, which is known to affect multifocal ERGs.[18,19] Therefore, comparing the condition of blue-light filter with a reference condition of no filter would be biased and would not allow a specific assessment of the effect of wavelength-specific filtering on the multifocal ERG. To assess this effect in isolation would require a reference condition that would reduce the luminance equivalently to the blue-light filter but would do so independent of the wavelength. To determine such a neutral filter, the following steps were taken: (1) The transmission of the blue-light filter was weighted with the spectral sensitivity of the human visual system using the v-lambda correction[20] (Figure 1). (2) The integral of the respective transmissions was calculated and the effective luminance transmission determined as 78.0%. (3) The transmission of a neutral filter that would yield a close match in

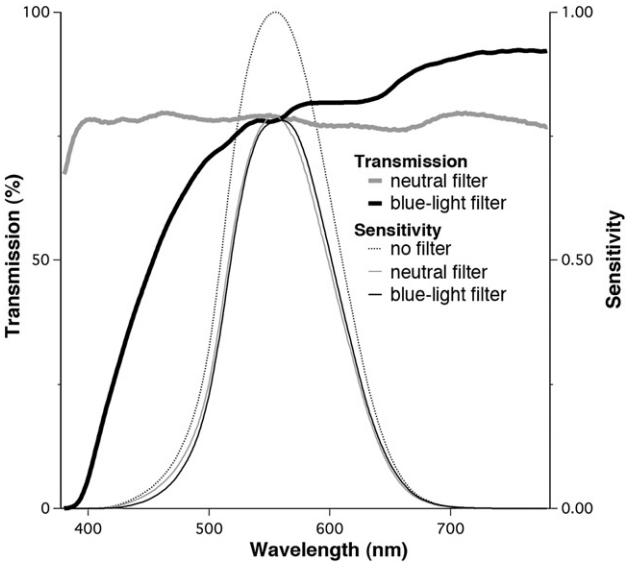

Figure 1. Filter characteristics. Wavelength-dependent transmission with the blue-light filter and the neutral filter and the respective sensitivities derived from the v-lambda curve (ie, the no-filter condition).

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terms of luminance reduction was determined. The neutral filter chosen as reference condition had a transmission close to 78.0% (ie, 78.2%).

Stimulation

A visual-evoked potential recording system (Versis 5.01.10X, Electro-Diagnostic Imaging, Inc.) was used for stimulus delivery and electrophysiologic recordings. With the chin on a chinrest, the patient viewed the stimuli presented at a distance of 40 cm on a P45 phosphor computer monochrome monitor (MDG403, Philips Electronics N.V.) driven with a frame rate of 75 Hz and fixated on a central black cross (2 degrees diameter). The visual stimulus was presented on a gray background (104 candelas [cd]/m^2). The stimulus covered 35 degrees of visual angle (diameter) and comprised 61 hexagons scaled with eccentricity (stretch factor 21.3). Thus, multifocal ERGs were recorded for 61 single visual-field locations. The hexagons were stimulated independently with an M-sequence. An M-sequence consists of a pseudorandom succession of 0 and 1 states, with state 0 equaling no flash (1.5 cd/m^2) and state 1 equaling flash (206 cd/m^2). An M-sequence length of 2^{15} 1 steps, with each step lasting 13.33 milliseconds, was used, resulting in a total recording time of 7:17 minutes per block. The blocks were subdivided into 16 overlapping segments, each lasting about 27 seconds, to alleviate steady fixation during the actual recordings. Recording segments contaminated by disturbances (eg, blinks or fixation instabilities) were discarded and replaced by an acceptable repetition of the segment.

Stimuli were viewed binocularly to guarantee stable fixation. Both eyes were best corrected for the viewing distance with trial lenses. Recordings were performed under mydriasis achieved with tropicamide 0.5% (Mydrum), and local anesthesia of oxybuprocaine hydrochloride (Novesine) was applied to the eye before electrode application. The eyes were kept light adapted at room illumination before recording. The patients viewed the stimuli through filters inserted in trial frames, and multifocal ERGs were recorded under 2 conditions: neutral filter and blue-light filter. The recording sessions lasted approximately 1 hour, including preparation and breaks. A single recording session comprised 2 blocks of 7:17 minutes each, 1 for each stimulus condition (ie, for neutral filter and blue-light filter). Two sessions were performed for each patient. To minimize sequential effects, the order of the 2 conditions was pseudorandomized for the first session and then reversed in the second session.

Multifocal Electroretinography

Recordings Multifocal ERGs were recorded in accordance with the International Society for Clinical Electrophysiology of Vision (ISCEV) standard.[21] The signals were recorded with a low-mass conductive thread corneal electrode[22] referenced to the ipsilateral canthus. The signal was amplified by 50 000 with a physiological amplifier (Grass Model 12, Astro-Med, Inc.), band-pass filtered (low-frequency cutoff, 10 Hz; high-frequency cutoff, 300 Hz), and sampled at 1200 Hz.

Analysis First-order kernels were extracted using the multifocal ERG recording system. As recommended for multi-focal ERG analysis with this recording device, 2 iterations of the artifact removal available in the system were applied. All subsequent analyses were performed with purpose-designed tools written in Igor Carbon software (version 6.00, WaveMetrics, Inc.). Traces were digitally filtered (low-pass cutoff, 100 Hz). The baseline was defined as the mean value of the averaged trace from 0 millisecond before to 10 milliseconds after stimulus onset. This value was subtracted from the traces before depiction and used as zero reference for peak measurements. To assess eccentricity-dependent effects, the traces were averaged across all responses in an eccentricity bin (number of traces contributing to each of the 5 eccentricity bins from center to periphery; that is, 1, 6, 12, 18, and 24). Peaks were defined according to the ISCEV standard[21] as follows: N1 and N2 were the first negative deflection and second negative deflection, respectively, and P1 was the first positive deflection. Peak amplitudes were determined for N1 as the difference between the N1 amplitude and baseline, for P1 as the difference between the P1 and N1 amplitude, and for N2 as the difference between the N2 and P1 amplitude.

Table 1. Patient characteristics.

Pt	Sex	Age (Y)	IOL*	CDVA (Snellen) Right Eye	CDVA (Snellen) Left Eye	Postop Time (Mo)
1	M	48	AR40e	20/50	20/20†	6
2	M	52	VA60BB	20/25†	20/20	28
3	F	56	VA60BB	20/20†	20/15	22
4	F	61	VA60BB	20/33	20/20†	16
5	F	63	AR40e	20/25†	20/29	55
6	M	64	AR40e	20/15	20/20†	40
7	M	66	AR40e	20/25	20/20†	17
8	F	66	SA60AT	20/22†	20/29	18
9	M	67	VA60BB	20/20	20/20†	12
10	F	70	VA60BB	20/33	20/20†	30
11	F	72	AR40e	20/25	20/20†	17
12	M	72	VA60BB	20/40	20/33†	31
13	F	72	VA60BB	20/29	20/33†	24
14	F	73	VA60BB	20/25†	20/25	14
15	F	73	VA60BB	20/20†	20/25	10
16	F	73	AR40e	20/50	20/50†	30
17	M	74	VA60BB	20/25†	20/25	14
18	F	75	VA60BB	20/33†	20/33	24
19	F	75	AR40e	20/25†	20/20	19
20	M	75	VA60BB	20/25†	20/15	12

CDVA = corrected distance visual acuity; IOL = intraocular lens; Pt = patient
*AR40e, Abbott Medical Optics, Inc.; VA60BB, Hoya Surgical Optics GmbH; SA60AT, Alcon, Inc.
†Eye in which recordings were taken

Statistical Analysis

Trace similarity for the 2 filter conditions was assessed with a correlation analysis. In this analysis, trace shapes were compared by correlating trace pairs obtained for identical visual field locations in a time window of 0 to 60 milliseconds after stimulus onset. For each quantitative comparison, this approach yielded 1220 (20 patients × 61 visual field locations) Pearson correlation coefficients (range −1.0 to +1.0).

The significance of the differences between the 2 stimulus conditions was evaluated with 2-factor repeated-measures

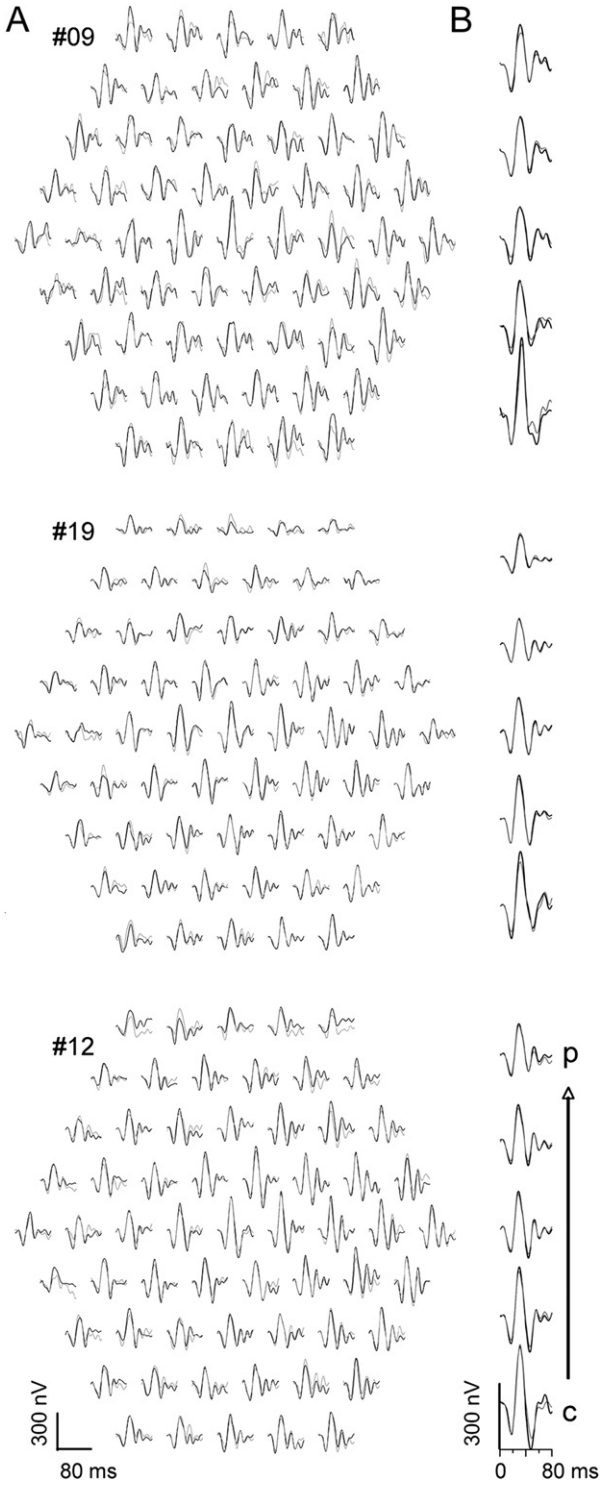

Figure 2. Individual multifocal ERG traces of 3 patients with different visual acuities (#09: 20/20; #19: 20/25; #12: 20/33). *A*: Trace arrays. Traces are depicted as left-eye recordings for all patients (ie, mirrored across the vertical meridian for patient 19 because the recordings are from the right eye). Thus, an indication of an amplitude reduction induced by the blind spot is evident at a visual field location at the horizontal meridian of the left hemifield. *B*: Traces averaged according to eccentricity. A high degree of similarity is evident for the traces for the 2 filter conditions (neutral filter, *gray*; blue-light filter, *black*).

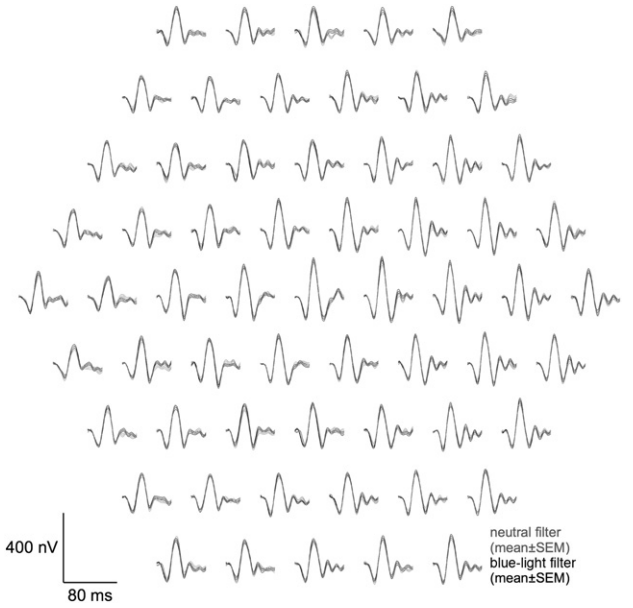

Figure 3. Grand mean traces (±SEM) (N = 20) as a reprojection to their corresponding visual field locations. Before averaging, the traces from the right eye (n = 10) were mirrored across the vertical meridian so that all traces appear to be obtained from the left eye.

analysis of variance (ANOVA) using SigmaStat software (version 3.5, Systat Software, Inc.). Thus, the factors of filter (neutral filter versus blue-light filter) and of eccentricity (5 eccentricities) and their interaction were assessed to determine their effect and interaction on individual peak amplitudes and latencies determined in a single-peak analysis. Significant effects were specified post hoc with paired *t* tests corrected for multiple testing using a sequential Bonferroni correction.[23] The mean amplitude and latency values are ± SEM.

An analysis of the statistical power of the approach based on *t* statistics was performed. The aim was to estimate the filter condition–dependent effect sizes in the single-peak analysis that could be shown with the design of the present study. The minimum detectable effect size between the 2 conditions was calculated from the scatter of the obtained single-peak measures for each stimulus eccentricity used; a significance criterion of $P < .05$ (Bonferroni corrected) was applied.

RESULTS

Twenty eyes (10 left) of 20 patients (12 women) with a median age of 71 years (range 48 to 76 years) were evaluated. Table 1 shows the patients' characteristics. The multifocal ERG recordings were performed a median of 18.5 months (range 6 to 55 months) after surgery. The median Snellen corrected distance visual acuity in the measured eyes was 20/24 (range 20/50 to 20/15).

Typical multifocal ERGs were obtained under neutral-filter and blue light-filter conditions. Figure 2 shows trace arrays in 3 eyes and Figure 3, the grand mean traces (across 20 patients for each of the 61 stimulus locations). The figures show the distinct

multifocal ERG components (ie, N1, P1, and N2 components) for each stimulus location. There were no gross differences in trace shapes between the 2 stimulation conditions. This was corroborated by a quantitative comparison of the trace shapes using the correlation approach described in Patients and Methods. First, the correlations of 1220 response pairs for the same stimulation conditions were determined, but during different sessions (ie, first session and second session). This within-condition correlation served as a reference value for the trace similarity. The median correlation coefficients were 0.82 and 0.83 for the neutral-filter condition and blue light–filter condition, respectively. Subsequently, the correlation of 1220 response pairs obtained for the 2 conditions were determined for better comparability across the first session and second session. Respective values (as for the intra-condition correlation) were 0.83 and 0.81.

The above correlation means that the general multifocal ERG trace shape did not depend on the filter condition; thus, the typical multifocal ERG components were also obtained under the blue light–filter condition. Subsequently, a more sensitive quantitative analysis of these components was applied. The analysis was based on the evaluation of the amplitudes and implicit times of peaks N1, P1, and N2 for each patient under the 2 conditions. To enhance the validity of the peak identification in this peak analysis at the single patient level, the traces were averaged according to the eccentricity of the stimulus location. Thus, 5 eccentricity groups were obtained. Figure 4 gives an overview of the corresponding grand mean traces (mean across 20 patients ± SEM). Table 2 shows the quantitative results of the peak analysis based on the individual traces. Figure 5 depicts the individual peak amplitudes and implicit times under both conditions. The factor eccentricity was significant for all tests conducted ($P < .000001$). No significant interactions of eccentricity and filter were obtained. The factor filter reached significance for 2 comparisons. First, the averaged P1 amplitudes were greater for the blue-light filter than for the neutral filter (amplitude enhancement averaged for eccentricities, 4.4%). In the corresponding ANOVA, the factor filter was of weak significance ($P = .033$) (Table 2). Sequential Bonferroni corrected post hoc t tests showed a significant difference in eccentricity E3 ($P \leq .003$; amplitude enhancement, 6.9%). This suggests that the P1 amplitude can be significantly enhanced for the blue-light filter. The second significant comparison for the factor filter was N2 implicit times, which were smaller with the blue-light filter than with the neutral filter (implicit time reduction averaged for eccentricities, 0.42 millisecond). In the corresponding ANOVA, the factor filter was of weak significance ($P = .030$); however, sequential Bonferroni corrected post hoc t tests showed no pairwise significant effects.

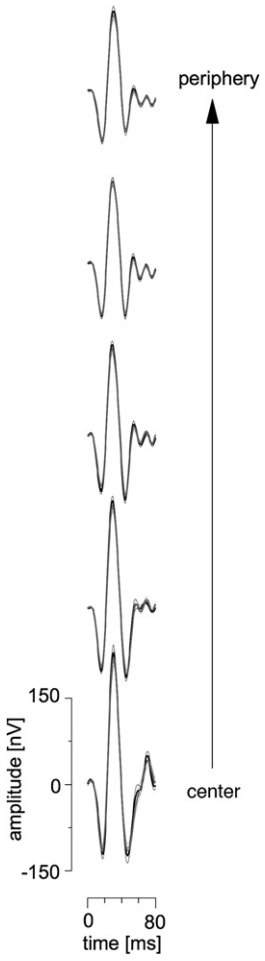

Figure 4. Grand mean traces (±SEM) (N = 20) averaged according to eccentricity (neutral filter, *gray*; blue-light filter, *black*).

The analysis of the statistical power showed that the approach of this study allowed, on average, the detection of amplitude changes on the order of 7% (for P1 and N2) and 14% (N1) and of latency changes by 0.7 millisecond, 0.8 millisecond, and 1.0 millisecond for N1, P1, and N2, respectively. The minimal detectable effect sizes were slightly higher for central responses than for those from other eccentricities. This is because a single multifocal ERG trace per patient contributed to the central response and ring averages were used for the other eccentricities. Thus, the scatter of the respective measures was greater for the central response.

DISCUSSION

Typical multifocal ERGs were obtained with neutral filters and blue-light filters. The general trace shape and most measures of amplitudes and implicit times of multifocal ERG components were unaffected by

Table 2. Mean amplitudes and implicit times for the main multifocal ERG peaks in 5 eccentricity ranges (N = 20).

	Eccentricity* (Mean ± SEM)				
Peak/Filter	E1	E2	E3	E4	E5
Peak N1					
Amplitude (nV)					
Neutral	−122.6 ± 8.4	−100.7 ± 5.4	−85.2 ± 4.5	−85.6 ± 5.0	−85.4 ± 5.7
Blue	−129.5 ± 11.3	−107.0 ± 5.1	−92.7 ± 6.0	−88.4 ± 4.7	−84.9 ± 5.2
Implicit time (ms)					
Neutral	16.75 ± 0.38	16.33 ± 0.28	16.08 ± 0.24	16.67 ± 0.20	17.42 ± 0.19
Blue	17.58 ± 0.38	16.38 ± 0.20	15.88 ± 0.19	16.71 ± 0.20	17.29 ± 0.18
Peak P1					
Amplitude (nV)					
Neutral	357.9 ± 22.1	292.0 ± 13.8	246.4 ± 11.7†	237.5 ± 12.6	226.8 ± 14.4
Blue	376.3 ± 23.1	306.7 ± 14.9	263.3 ± 13.0†	241.5 ± 13.0	234.7 ± 14.6
Implicit time (ms)					
Neutral	31.13 ± 0.43	29.83 ± 0.42	29.21 ± 0.32	29.75 ± 0.37	30.96 ± 0.38
Blue	30.96 ± 0.56	29.67 ± 0.34	29.17 ± 0.38	29.83 ± 0.40	30.96 ± 0.37
Peak N2					
Amplitude (nV)					
Neutral	−374.4 ± 23.2	−314.0 ± 15.9	−270.7 ± 13.2	−243.7 ± 13.9	−215.2 ± 16.4
Blue	−387.6 ± 23.3	−323.7 ± 17.5	−286.0 ± 13.7	−246.5 ± 15.3	−222.4 ± 16.9
Implicit time (ms)					
Neutral	49.29 ± 0.95	46.46 ± 0.57	44.79 ± 0.37	44.75 ± 0.37	45.13 ± 0.40
Blue	47.83 ± 0.76	46.21 ± 0.56	44.63 ± 0.36	44.63 ± 0.33	45.04 ± 0.40

N1 = first negative deflection; N2 = second negative deflection; P1 = first positive deflection
*Eccentricities from visual field center to periphery (see Patients and Methods)
†Statistically significant

the applied spectral weighting of the visual stimuli with filter elements. Thus, we conclude the multifocal ERG was largely unaffected by the blue-light filter and that if there were changes, they were subtle. Essentially, the data suggest an amplitude enhancement for the P1 component with blue-light filters, particularly at eccentricity E3. The 6.9% amplitude enhancement is comparatively small. The use of a cathode ray tube for stimulation must be considered a potential source of the observed effect. Rather than representing a continuous spectrum, white visual stimuli presented on a monitor will comprise emission maxima in the spectrum. In the present study, a lack of short wavelengths in the spectrum would lead to higher effective luminance under the blue-light filter condition than under the neutral filter condition and thus be expected to entail greater multifocal ERG amplitudes under the blue-light filter condition. Although the phosphor P45, which was used in the present study, has an absolute emission maximum at a wavelength of 550 nm, it has sizable relative maxima in the short wavelength range, particularly at 415 nm and 440 nm; that is, 65% and 35% of the maximal peak, respectively.[24] As a consequence, a physiologic cause of the slight amplitude enhancement observed appears more plausible. The spectral composition of the stimulus for the blue-light filter is shifted to the long wavelength range, which is expected to drive L-cones stronger than M-cones. The L-cone to M-cone ratio and the L-cone to M-cone multifocal ERG amplitude ratios are greater than 1.0.[25] A previous study[26] found a multifocal ERG amplitude ratio of 2.2 for the P1 component and of 1.6 for the N1 component. Shifting the spectral composition of a visual stimulus to the long wavelength range, as in the present study under the blue-light filter condition, should therefore result in a slight increase in multifocal ERG amplitudes, particularly for the P1 component, as the data in our study imply.

Several psychophysical studies[5–13] have found that blue-light filtering has no significant effect on visual performance. Thus, the sensitivity of the experimental approach might be crucial in finding potential subtle effects. In our study, we sought to optimize the sensitivity of the approach. First, we performed an intraindividual comparison in the same eye of each patient, reducing the effect of interindividual variability. Second, we averaged data from 2 multifocal ERG recordings for each condition. These repetitions were collected in different sessions to reduce patient fatigue during the course of a single session. Third, to cancel sequential effects, we reversed the order of conditions between the first session and the second session.

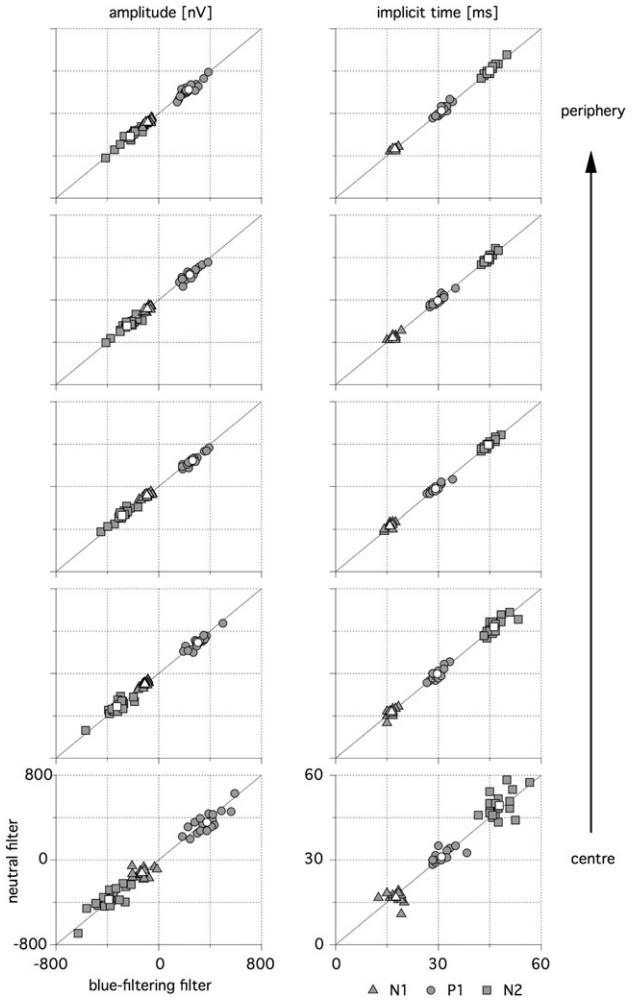

Figure 5. Peak amplitudes and implicit times for the peaks N1, P1, and N2 at each of the 5 stimulated eccentricities (neutral filter versus blue-light filter). The filled symbols represent individual data points and the white symbols, the mean ± SEM across 20 patients (*triangles* = N1; *circles* = P1; *squares* = N2). Standard errors are often around the magnitude of the symbol size.

Fourth, to reduce the effect of fixation instabilities, the stimuli were presented with best refractive correction to the dilated eye and the fellow eye during the recordings. An analysis of the statistical power of our approach showed that it could detect amplitude changes between 7% and 14% and latency changes of 1 millisecond or less. Finally, the experiments were performed in eyes with a colorless IOL. This approach excluded the effects of crystalline lens aging on the spectral composition of the light reaching the retina.[1] In addition, it was possible to assess the effects in the relevant patient group; that is, in patients with an aged visual system who required implantation of an IOL. Given the above precautions, we conclude that the relevant effects induced by the experimental manipulation are confined to the ones detailed above.

Our study specifically aimed to evaluate the effect of wavelength-specific filtering at the retinal input stage. The results imply subtle effects that are likely associated with the retinal network comprising photoreceptors, horizontal cells, and bipolar cells and a potential additional contribution of the inner retina. It is now of interest to understand whether processing at the retinal ganglion cell level and by the extraretinal circuitry is affected by blue-light filtering. At this stage, wavelength-dependent processing might be altered by the change in the spectral composition of the visual stimulus. Moreover, long-term blue-light filtering might trigger adaptation processes. The present study assessed the short-term effects of blue-light filtering on retinal activity. It would be beneficial to address long-term effects in a follow-up study with an appropriate design.

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