Effect of blue-light filtering on multifocal visual-evoked potentials

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PURPOSE: To perform an objective functional assessment of the impact of blue-light filters on cortical processing to evaluate the potential side effects of the filters on higher tier visual function at the neural level.

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

DESIGN: Cohort study.

METHODS: Multifocal pattern-reversal visual-evoked potentials (multifocal VEPs) were recorded monocularly in pseudophakic patients with a clear intraocular lens (IOL) under 2 conditions: (1) stimulus perception through a yellow filter with the filter characteristics of an AF-1 YA-60BB IOL (blue filtering); (2) stimulus perception through a neutral filter that homogeneously attenuates the effective stimulus intensity as under the blue-light filtering condition but independent of the wavelength (neutral filtering). Second-order kernel multifocal VEPs were extracted for 60 visual field locations, and amplitude and latency effects were determined for 6 stimulus eccentricities.

RESULTS: The study evaluated 20 patients. Typical multifocal VEPs were obtained for the blue-light and neutral filtering conditions at all eccentricities. No significant effects on amplitudes were obtained, and a subtle latency effect (<0.5 millisecond delay for neutral filtering; \( P < 0.02 \)) did not reach significance in an eccentricity-specific analysis.

CONCLUSIONS: The induced short-term change in the spectral composition of the visual stimulus left neural activity at the level of the primary visual cortex largely unaffected, providing an objective account of the integrity of visual processing under this condition.

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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. To reduce a potential risk for photic retinopathy, IOLs that eliminate ultraviolet radiation are commonly implanted in cataract surgery; IOLs that eliminate an even broader range in the short-wavelength spectrum, known as yellow IOLs, might reduce this risk further. Although the implementation of blue-light filtering IOLs might provide retinal, and in particular macular, protection, side effects of blue-light filtering on visual processing might arise. The performance in subjective visual tests, specifically contrast sensitivity and color perception, appears to be little or not affected by blue-light filtering. Furthermore, the neural activity of the retina assessed with a multifocal electroretinogram (ERG) remained largely unchanged by short-term changes in the spectral composition of the stimulus exerted by blue-light filtering. Higher processing stages, such as the retinal ganglion cell level and the extraretinal and cortical circuitry, are to some degree specialized for wavelength-dependent processing. As a result, they might be more strongly affected by changes in the spectral composition of the visual stimulus induced by blue-light filtering IOLs. Thus, effects at the level of the visual cortex would not be unexpected and highlight the consequences of blue-light filtering on visual perception. It is therefore important to understand whether blue-light filtering has sizable effects on cortical signals.
The ideal tool for spatially resolved assessment of the functional integrity of the visual system at higher tier processing levels are multifocal visual-evoked potentials (VEPs).\textsuperscript{15-17} The multifocal VEP reflects activity generated predominantly in the primary visual cortex.\textsuperscript{16,17} It allows the simultaneous derivation of cortical responses from a large number of visual field locations within a short interval. Thus, visual field topographies of cortical function can be obtained within a few minutes of recording time. The aim of the present study was to isolate the effect of blue-light filtering on processing in the visual cortex. This effect was assessed in a spatially resolved manner using the multifocal VEPs.

Similar to methodology in our previous multifocal ERG study,\textsuperscript{14} this study evaluated patients with a colorless IOL with a paradigm that allowed intraindividual comparisons to increase the sensitivity of the approach. The multifocal VEPs were recorded for stimuli viewed through a blue-light filter and through an equivalent neutral filter. The spectral composition of the stimulus was demonstrated to leave the multifocal VEPs largely unaffected, which provides the first objective account of the integrity of higher tier visual processing under this condition.

**PATIENTS AND METHODS**

**Rationale**

The applied rationale followed that in the previous study of the effect of blue-light filtering on the multifocal ERG.\textsuperscript{14} The effect of wavelength-specific filtering on multifocal VEPs was assessed using a filter with the absorption characteristics of an AF-1 YA-60BB IOL (Hoya Corp.), a condition termed blue filtering in this paper. This filter preferentially suppresses the short-wavelength range but also has an effect on the remaining visible spectrum (for specific filter characteristics, see Hoffmann et al.\textsuperscript{14}). Thus, the spectral composition of the stimulus and the actual stimulus luminance are changed, which is known to affect multifocal VEPs.\textsuperscript{18} Therefore, comparing the condition of blue filtering with a reference condition of no filter would be biased and would not allow specific assessment of the effect of wavelength-specific filtering on multifocal VEPs. To assess this effect in isolation, a reference condition is needed that reduces the luminance to a level equivalent to blue filtering but independent of the wavelength. This condition is termed neutral filtering in this paper. The neutral filter was determined using the following steps: (1) The transmission of the blue-light filter was weighted with the spectral sensitivity of the human visual system using the v-lambda correction.\textsuperscript{19} (2) The integral of the respective transmissions was calculated and the effective luminance transmission determined to be 78.0%. (3) It was determined which transmission of a neutral filter would yield a close match in terms of luminance reduction. The neutral filter chosen for the reference condition had a transmission close to 78.0%, namely 78.2%.

**Patients**

All patients gave their informed written consent before the study. The procedures followed the tenets of the Declaration of Helsinki,\textsuperscript{20} and the Ethics Committee, University of Magdeburg, Germany, approved the protocol. Exclusion criteria were a history of ocular trauma, retinal surgery, intraocular infection, anterior or posterior synchiae, clinically significant macular edema, age-related macular degeneration, epiretinal gliosis, diabetic retinopathy, corneal opacity, manifest glaucoma, CDVA worse than 20/50, and instable fixation. Patients with strabismus were also excluded.

Multifocal VEP recordings were performed monocularly at least 6 months after cataract surgery with implantation of a colorless spherical IOL. The median decimal visual acuity in these eyes was converted to Snellen notation.\textsuperscript{21}

**Procedure**

Stimuli were viewed monocularly corrected for the viewing distance.\textsuperscript{22} For this purpose, an infrared eye camera refraction system (Electro-Diagnostic Imaging, Inc.) was used that also provided a magnified video image of the coaxial view of the pupil of the stimulated eye to monitor ocular alignment and fixation stability during recordings. The patients viewed the stimuli through filters inserted in trial frames, and multifocal VEPs were recorded for 2 conditions: neutral filtering and blue filtering. The recording sessions, including preparation and breaks, did not exceed 1.5 hours. A single recording session comprised 4 blocks lasting 7.17 minutes, 2 for each stimulus condition (ie, for neutral filtering and blue filtering) presented in a counterbalanced design to minimize sequential effects.

**Electrophysiologic Recordings**

The multifocal VEPs were recorded from 3 gold cup electrodes referenced to the inion (Iz) using a VEP recording system (Veris Science, version 5.01.10X, Electro-Diagnostic Imaging, Inc.). Electrodes were placed 4 cm left and right (OL and OR, respectively) of the location 1 cm above the Iz and at Oz (occipital midline).\textsuperscript{23} The electroencephalogram was amplified with a physiological amplifier, band-pass filtered (low and high frequency cutoffs 3 Hz and 100 Hz, respectively), and digitized at 1200 Hz. Supported by a chin rest, patients viewed the stimuli that were presented at a distance of 38 cm on a computer monitor driven with a frame rate of 75 Hz. They were asked to fixate on a central black cross. The stimulus display, a circular dartboard pattern (diameter 44 degrees, mean luminance 85 candelas/m\textsuperscript{2}, contrast 97%), was subdivided into 60 individual fields, each comprising a checkerboard of 4 checks × 4 checks. The radial extent of the fields was scaled with eccentricity from 1.6
Multifocal Visual-Evoked Potentials Analysis

Second-order kernels were extracted using the above VEP recording system. All subsequent analyses were performed with Igor software (version 6, Wavemetrics, Inc.). For recordings of either eye, the 3 physical derivations were referenced as in previous studies, yielding 6 derivations. The traces were digitally low-pass filtered with an upper frequency cutoff of 30 Hz, and the records from the 2 blocks for each stimulus were averaged. Before analysis, the visual field locations for the stimulation of the right eye (ie, for 9 patients) were left–right flipped (ie, traces from the left visual hemifield were swapped with those of the corresponding position in the right hemifield) and the channels OL and OR were swapped. Thus, all records looked as though they were recorded for stimulation of the left eye, which simplified comparisons across patients.

To assess signal presence, the root mean square (RMS) of the multifocal VEPs in a signal (45 to 150 ms) and a noise window (325 to 430 ms) was determined. With these RMS values, the signal-to-noise ratio (SNR) was evaluated as described by Zhang et al. This SNR definition deviates slightly from the standard SNR definition because of the subtraction of 1 from the SNR and is therefore termed SNR'. An estimate of false-positive rates was obtained from the distribution of SNR' values in the noise window, showing that the probability of an SNR' of 1 or more to be part of the noise distribution was smaller than 2.4%. Therefore, an SNR' threshold of 1 was applied to exclude, in accordance with established procedures, silent visual field locations (ie, without recordable signals) from the analyses. To reconstruct the visual field topography and for subsequent analyses, the maximum suprathreshold response at each visual field location was selected out of the 6 derivations. The multifocal VEPs for both conditions were selected for this maximum derivation. Trace similarity of and latency differences in the obtained trace pairs were assessed for each visual field location separately for each patient by cross correlating the suprathreshold trace pairs within a time window of ±20 milliseconds. The mean correlation coefficient and standard deviation (SD) was determined after Fisher z-transformation and subsequently transformed back for clarity.

Statistical Analysis

The significance of the experimental effects was assessed using Student t test and, if not otherwise stated, corrected for multiple testing using the sequential Bonferroni correction. Mean values for amplitude measures are shown ± the standard error of the mean (SEM). An analysis of the statistical power of the approach based on t statistics was performed. The aim of this analysis was to estimate the filter-induced effect sizes that could have been shown with the design of the present study. The minimum detectable percentage change between the 2 conditions was calculated from the scatter of the obtained RMS ratios and SNR' ratios (blue filtering:neutral filtering) for each of the 3 physical derivations, applying a significance criterion of a P value less than 0.05.

RESULTS

The study enrolled 20 patients (14 women) with a median age of 72 years (range 49 to 76 years). Table 1 gives an overview of the patients, including the implanted IOL type. Multifocal VEP recordings were performed in the respective eye (9 right eyes) a median of 31.5 months (range 6 to 96 months) after cataract surgery. Of 1200 measured multifocal VEPs (20 subjects × 60 visual field locations), 1074 suprathreshold multifocal VEPs were entered into the analysis. The median Snellen acuity in the operative eye, converted from decimal visual acuity, was 20/26 (range 20/44 to 20/15).

Typical multifocal VEPs were obtained for the neutral-filtering and the blue-filtering conditions. Figure 1 shows the visual field topography of the multifocal VEPs for 4 patients, covering the range of visual acuities. No gross differences of the trace shapes and

### Table 1. Patient overview.

<table>
<thead>
<tr>
<th>Pt</th>
<th>Sex</th>
<th>Age (Y)</th>
<th>IOL*</th>
<th>CDVA</th>
<th>Postop Time (Mo)</th>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>49</td>
<td>AR40e</td>
<td>RE 20/50 LE 20/33</td>
<td>30</td>
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<tr>
<td>2</td>
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<td>57</td>
<td>VA60BB</td>
<td>RE 20/40 LE 20/16</td>
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<tr>
<td>3</td>
<td>F</td>
<td>62</td>
<td>VA60BB</td>
<td>RE 20/32 LE 20/26</td>
<td>28</td>
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<tr>
<td>4</td>
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<td>64</td>
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<td>RE 20/40 LE 20/29</td>
<td>67</td>
</tr>
<tr>
<td>5</td>
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<td>AR40e</td>
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<td>43</td>
</tr>
<tr>
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<td>F</td>
<td>67</td>
<td>SA60AT</td>
<td>RE 20/25 LE 20/17</td>
<td>6</td>
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<tr>
<td>7</td>
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<td>VA60BB</td>
<td>RE 20/32 LE 20/17</td>
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<tr>
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<td>11</td>
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<tr>
<td>9</td>
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<td>70</td>
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<td>10</td>
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<tr>
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<td>73</td>
<td>VA60BB</td>
<td>RE 20/24 LE 20/44</td>
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<tr>
<td>12</td>
<td>F</td>
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<td>AR40e</td>
<td>RE 20/25 LE 20/22</td>
<td>53</td>
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<tr>
<td>13</td>
<td>M</td>
<td>73</td>
<td>VA60BB</td>
<td>RE 20/40 LE 20/26</td>
<td>42</td>
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<tr>
<td>14</td>
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<td>73</td>
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<td>37</td>
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<tr>
<td>15</td>
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<tr>
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<td>F</td>
<td>76</td>
<td>VA60BB</td>
<td>RE 20/25 LE 20/33</td>
<td>36</td>
</tr>
</tbody>
</table>

CDVA = corrected distance visual acuity; IOL = intraocular lens; Pt = patient
*AR40e, Abbott Medical Optics, Inc.; VA60BB, Hoya Surgical Optics GmbH; SA60AT, Alcon, Inc.; H30P, Polytech GmbH
†Stimulated eye
amplitudes were evident under the 2 stimulation conditions. This was tested quantitatively in subsequent analyses across the entire patient sample. First, potential effects on the RMS and SNR were assessed. For this purpose, the suprathreshold SNR and RMS were averaged separately for the 3 physical derivations within each patient. Subsequently, the logarithmized SNR ratio and RMS ratio—that is, log(blue filtering:neutral filtering)—were determined for each patient. For these ratios, a determination was made as to whether there was an effect of blue filtering across patients; no significant effects were detected (Table 2). To assess eccentricity-specific effects, the same analysis was performed within each eccentricity bin (Figure 2). Again, no significant effects were detected, indicating that the response magnitudes of the multifocal VEPs were not affected by spectral filtering. Second, potential effects on response latency were assessed. For this purpose, cross correlations of the multifocal VEPs for a given visual field location were computed for the 2 stimulation conditions as described in Patients and Methods. A mean correlation coefficient of 0.967 was obtained with an upper SD and a lower SD of 0.023 and 0.085, respectively. Figure 3 shows the visual field topography of the correlation coefficients for the 4 patients in Figure 1. The

Figure 1. Individual multifocal VEP visual field topographies of 4 representative patients with different visual acuities (patient 09, 20/16; patient 20, 20/25; patient 16, 20/33; patient 11, 20/44) reconstructed from 6 derivations. The traces are depicted as left-eye recordings in all patients and spatially arranged as a reprojection of the signals to the visual field locations that evoked them. Note that the traces from different eccentricities are arranged in an equidistant manner, while the actual stimulus layout is approximately m-scaled. A high degree of similarity is evident for the traces between the 2 filter conditions, which are spaced vertically for clarity (neutral filtering: gray; blue filtering: black).
cross correlation allowed the calculation of the delay between the traces for the 2 conditions. Across all eccentricities, there was a subtle sub-millisecond multifocal VEP delay of 0.47 ± 0.18 millisecond (mean across 20 patients ± SEM; P < 0.02) for neutral filtering compared with blue filtering, which failed to reach significance when assessed for any individual eccentricity (Table 2 and Figures 1 to 2).

**DISCUSSION**

Typical multifocal VEPs were obtained for neutral filtering and blue filtering. The general trace shape and multifocal VEP amplitude measures were unaffected by the applied spectral weighting of the visual stimuli with filter elements. Effects on response latencies were in the sub-millisecond range and did not reach significance when assessed in an eccentricity-dependent analysis. This very subtle latency effect might be associated with the shift in the spectral composition of the blue-filtering stimulus to the long wavelength range, as was previously discussed in a study of the effect of blue filtering on multifocal ERGs. Alternatively, such a latency effect could arise from small residual differences in overall luminance between the 2 stimulation conditions. Great care was taken to equate the luminance for the 2 stimulus conditions with an approach that was based on the measured transmission.

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Table 2. Mean RMS and SNR ratios (blue filtering:neutral filtering) for the 3 physical derivations (N = 20).*

<table>
<thead>
<tr>
<th>Derivation Measure</th>
<th>Mean</th>
<th>+ SEM</th>
<th>− SEM</th>
<th>P Value</th>
<th>Detection Limit [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR vs Iz RMS ratio</td>
<td>0.981</td>
<td>0.025</td>
<td>0.024</td>
<td>.45</td>
<td>5.1</td>
</tr>
<tr>
<td>SNR ratio</td>
<td>0.991</td>
<td>0.020</td>
<td>0.020</td>
<td>.67</td>
<td>4.1</td>
</tr>
<tr>
<td>Oz vs Iz RMS ratio</td>
<td>0.998</td>
<td>0.013</td>
<td>0.013</td>
<td>.90</td>
<td>2.7</td>
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<tr>
<td>SNR ratio</td>
<td>1.027</td>
<td>0.017</td>
<td>0.017</td>
<td>.12</td>
<td>3.4</td>
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<tr>
<td>OL vs Iz RMS ratio</td>
<td>1.009</td>
<td>0.025</td>
<td>0.024</td>
<td>.70</td>
<td>4.9</td>
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<tr>
<td>SNR ratio</td>
<td>1.009</td>
<td>0.037</td>
<td>0.035</td>
<td>.80</td>
<td>7.2</td>
</tr>
</tbody>
</table>

*Ratios of suprathreshold visual field locations (SNR > 1.0, see Patients and Methods section) were converted to log values before (1) averaging, (1) calculation of the SEM, and (3) significance tests (t tests) assessing the difference of the log(ratio) from 0. Because none of the P values reached significance, a correction for multiple testing was obsolete. For better readability, mean values and measures for the scatter (+SEM and −SEM) were delogarithmised for inclusion in the table. An effect of the filtering condition would result in significantly different mean values from 1.0 (>1.0 and <1.0 for greater and smaller blue-filtering responses, respectively). The results in a power analysis are shown in the Detection Limit column, giving the minimum percentage signal change that would have been detected with a significance criterion of P < 0.05.

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Figure 2. Amplitude measurements for each of the 6 eccentricity bins for the 3 physical derivations used (mean ± SE; only suprathreshold visual field locations entered the analysis, the respective number of subjects in whom at least 1 such location contributed to the eccentricity bin is indicated in A next to the x-axis [n = 16 to 20, depending on derivation and eccentricity]). A: The SNR and RMS values for both stimulation conditions. B: The SNR and RMS ratios (blue filtering:neutral filtering) (c = central visual field eccentricity; OL = left location; OR = right location; Oz = occipital midline; p = peripheral visual field eccentricity; RMS = root mean square; SNR = signal-to-noise ratio).
Although this study specifically aimed to assess the effect of the change in the spectral composition of the visual stimulus, as a matter of course, the reduction in stimulus luminance exerted by blue filtering is expected to affect multifocal VEPs, namely by increasing response latencies. Furthermore, the design of the present study allowed the assessment of the short-term effects of blue filtering on cortical activity. Because processes of adaptation might be triggered by long-term blue filtering, it would be intriguing to address long-term effects in a follow-up study with an appropriate study design.

The present study specifically sought to assess the effect of wavelength-specific filtering on neural activity at the level of the primary visual cortex, which is the main generator of the multifocal VEP. No relevant effects were found; thus, we present the first objective account of the integrity of visual processing after blue filtering at the cortical level. This report complements our previous multifocal ERG study, which found no relevant effects of blue filtering on the retinal network. Taken together, these 2 studies show that neural activity, in neither the retinal nor the extraretinal circuitry, is significantly affected by blue filtering, as reflected by the mass recordings.

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