Functional Magnetic Resonance Imaging to Assess the Neurobehavioral Impact of Dysphotopsia with Multifocal Intraocular Lenses

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Purpose: To investigate the association between dysphotopsia and neural responses in visual and higher-level cortical regions in patients who recently received multifocal intraocular lens (IOL) implants.

Design: Cross-sectional study.

Participants: Thirty patients 3 to 4 weeks after bilateral cataract surgery with diffractive IOL implantation and 15 age- and gender-matched control subjects.

Methods: Functional magnetic resonance imaging (fMRI) was performed when participants viewed low-contrast grating stimuli. A light source surrounded the stimuli in half of the runs to induce disability glare. Visual acuity, wavefront analysis, Quality of Vision (QoV) questionnaire, and psychophysical assessment were performed.

Main Outcome Measures: Cortical activity (blood oxygen level dependent [BOLD] signal) in the primary visual cortex and in higher-level brain areas, including the attention network.

Results: When viewing low-contrast stimuli under glare, patients showed significant activation of the effort-related attention network in the early postoperative period, involving the frontal, middle frontal, parietal frontal, and postcentral gyrus (multisubject random-effects general linear model (GLM), P < 0.03). In contrast, controls showed only relative deactivation (due to lower visibility) of visual areas (occipital lobe and middle occipital gyrus, P < 0.03). Patients also had relatively stronger recruitment of cortical areas involved in learning (anterior cingulate gyrus), task planning, and solving (caudate body). Patients reporting greater symptoms induced by dysphotic symptoms showed significantly increased activity in several regions in frontoparietal circuits, as well as cingulate gyrus and caudate nucleus (q < 0.05). We found no correlation between QoV questionnaire scores and optical properties (total and higher order aberration, modulation transfer function, and Strehl ratio).

Conclusions: This study shows the association between patient-reported subjective difficulties and fMRI outcomes, independent of optical parameters and psychophysical performance. The increased activity of cortical areas dedicated to attention (frontoparietal circuits), to learning and cognitive control (cingulate), and to task goals (caudate) likely represents the beginning of the neuroadaptation process to multifocal IOLs.
an important process in favorable multifocal IOL outcomes. However, no functional study addressing the human cerebral cortex in this setting has been done, to the best of our knowledge, following PubMed database searches conducted by using distinct combinations (with AND and OR operators) of the terms functional, lenses, magnetic resonance, multifocal, neuroadaptation, dysphotopsia, and neurobehavioral.

Functional magnetic resonance imaging (fMRI) has opened an unprecedented opportunity for studying brain activity in vivo. It is a noninvasive method based on the contrast between oxygenated and deoxygenated hemoglobin (blood oxygen level dependent [BOLD] signal) associated with neuronal activity. It has been used for the evaluation of dysphotopsia after complicated LASIK, amblyopia treatment outcomes, and visual plasticity in retinal disorders, such as macular degeneration and pigmented retinopathy.

In the present study, we used fMRI to evaluate dysphotopsia in patients who recently received bilateral multifocal lens implants. We analyzed the impact of a glare source on the visual cortex and in higher-level areas, that is, with a focus on task- and effort-related regions in the human brain. The purpose of this assessment is to understand whether objective measures of neural activity in the human brain can shed light on the pathophysiology of the difficulty created by a light source in patients with multifocal IOLs. If successful, this approach could lead to the discovery of neurobehavioral correlates of dysphotopsia.

Methods

Study Design and Groups

This cross-sectional study included 30 patients younger than 75 years of age who received bilaterally bifocal diffractive IOLs. Inclusion criteria were absence of surgical complications, preoperative sphere in either eye less than 6 diopters (D) in magnitude, less than 1.5 D of corneal astigmatism, regular topography, and no history of other ocular comorbidities, such as metallic foreign bodies, glaucoma, retinal diseases, previous corneal or intraocular surgery, pupil deformations, and amblyopia. Multifocal lenses (nontoric) were implanted binocularly with approximately a +3.00 addition. In addition, 15 subjects were recruited from the general ophthalmology clinic, with the following inclusion criteria: distance-corrected visual acuity (VA) ≥20/25 and normal ophthalmic examination (phakic subjects, without significant lens opacities, sphere in either eye <6 D in magnitude, regular topography, and no history of other comorbidities, such as metallic foreign bodies, glaucoma, retinal diseases, previous corneal or intraocular surgery, pupil deformations, and amblyopia). Subjects were chosen to match the ages and genders of patients in the multifocal group.

Before participating, all subjects were provided information about the study and given an information letter to be read at home (presenting the study as an effort to understand changes in the brain after cataract surgery). At the next follow-up appointment, the scope and objectives of the study were further explained, together with the clarification of any questions that might have arisen after reading the information sheet.

The study adhered to the Tenets of the Declaration of Helsinki and was approved by the ethical committee of the Faculty of Medicine of the University of Coimbra. All patients and controls were adequately informed and signed the informed consent form.

Ophthalmological Examination

At postoperative week 3 after the second eye surgery, patients underwent a complete ophthalmological examination consisting of the evaluation of uncorrected and corrected distance visual acuity, distance-corrected near visual acuity, corrected and uncorrected near visual acuity, uncorrected and distance-corrected intermediate visual acuity, slit-lamp examination, tonometry, and fundoscopy. The timing of this visit was scheduled to occur as soon as possible after surgery, at the same time allowing enough time for postoperative healing of the ocular structures.

Visual Acuity. Distance visual acuity was measured using Early Treatment Diabetic Retinopathy Study charts, and near visual acuity was measured with the Portuguese version of the Radner test (Radner-Coimbra Reading Charts). Interim vision was evaluated at 80 cm. All measurements were taken under photopic conditions (80 candela [cd]/m²).

Optical Properties. Total ocular and internal aberrations, Strehl ratio, and modulation transfer function (MTF) were evaluated with the iTrace (version 6.0.1, Tracey Technologies, Houston, TX). The iTrace combines an aberrometer with corneal topography. For wavefront analysis, it uses the ray-tracing principle, in which 256 near-infrared laser beams are projected sequentially into the eye. A Placido-based corneal topographer (Eyesys Vision, Inc., Houston, TX) mounted on the same device is used for topography. Corneal aberrations are calculated from topography data, and the internal aberrations are obtained by subtracting the corneal aberrations from those of the entire eye measured by the ray-tracing wavefront analyzer, using a built-in program. Three automatic wavefront acquisitions were obtained for each eye in a dark room: 1 wavefront combined with topography; 1 manual wavefront at 2.3, 4, and 5 mm (if possible); and 3 dilated manual wavefront acquisitions at 2, 3, 4, and 5 mm. The wavefront scans were reviewed, and the best-quality scan of the 3 manual measurements at 4 mm was selected for further analysis. Wavefronts were measured for a 4.0-mm optical zone after dilating the pupil. The following data of the total ocular, internal, and corneal optics were registered: the total root mean square (RMS), RMS of higher-order aberrations from third- to fifth-order Zernike coefficients, average MTF height, MTF at 10 cycles per degree (cpd), and Strehl ratio. The 10 cpd spatial frequency was chosen because both the psychophysical target used for contrast threshold discrimination and the fMRI imaging stimuli have a spatial frequency of 10 cpd.

Total RMS, MTF, and Strehl ratio values without spherically-cylindrical correction were extracted from the iTrace in operated patients. In controls, these parameters were selected with correction to come as close as possible to clinical reality and to be able to search for correlations between symptoms, optical properties, and functional outcomes. The same rationale was applied for psychophysical assessment and fMRI, during which patients in the multifocal IOL group wore no spectacle correction and controls had spectacle correction.

Quality of Vision Questionnaire. With the Validated Quality of Vision (QoV) questionnaire, subjects rated 10 visual symptoms (glare, haloes, starburst, hazy vision, blurred vision, distortion, double or multiple images, fluctuation, focusing difficulties, and difficulty in judging distance or depth perception). The first
7 symptoms have an associated picture to describe the visual symptom to improve patient understanding. The QoV questionnaire is formed by 3 separate subscales (frequency, severity, and bothersome). Raw questionnaire data were Rasch scaled to provide interval-level measurement properties.

Optical Coherence Tomography Scan Acquisition. Macular and optic nerve scans were acquired by trained technicians using the Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) and analyzed by one of the researchers to exclude retinal or optic nerve pathology contraindicating inclusion in the study.

Psychophysical Assessment

Psychophysical assessment consisted of a forced-choice detection test designed to determine the contrast threshold for each subject with the Method of Constant Stimuli. The stimulus was developed in MATLAB (Version R2014b; MathWorks, Natick, MA), using the Psychophysics Toolbox. It consisted of Gabor patches oriented at 90° with spatial phase of 180°, 2.5° of standard deviation (SD) size, spatial frequency of 10 cpd, 10 contrast levels, and mean luminance matching the background (20 cd/m²). Stimulus contrast was defined as the difference in luminance between the bright and dark grating bars divided by the sum and multiplied by 100 (Michelson contrast).

Each participant completed 2 experimental runs with a surrounding luminance light source of 13 cd/m² at 13° from the visual axis and 1 without. The glare source was introduced by means of a light-emitting diode light tape assembled on a square structure with a dimmer to regulate light intensity. The light source caused disability glare, confirmed by significantly higher-contrast detection thresholds when the lights were on, in both patients and controls (further details in “Results”). The complete glare setup was constructed with nonmagnetic magnetic resonance imaging (MRI)-compatible materials and was equal to the one used inside the magnetic resonance bore.

An experimental run consisted of 200 trials (20 trials for each contrast level). Each trial comprised a stimulation phase in which the Gabor appeared in the center of the screen during 500 ms, followed by a response/fixation period.

A Weibull function was used to fit to the psychometric data using a maximum likelihood procedure to estimate the contrast increment that would produce 80% correct performance. The threshold contrast and near threshold are obtained, for each run, taking the 50% and 75% points, respectively.

Functional Magnetic Resonance Imaging

Each participant performed two 3-dimensional (3D) anatomic magnetization—prepared, rapid-acquisition gradient echocardiography and 7 functional runs: 3 retinotopic measurements (to acquire detailed visual field mapping, discussed later) in a block paradigm, based on bar stimuli developed by Dumoulin and Wandell and 4 contrast discrimination tasks, in an event-related design. All participants were presented with the same randomized sequences.

Functional Task Description. Contrast discrimination tasks were performed in the scanner using Gabor stimuli as in the psychophysical assessment. The scans were performed both with (2 runs) and without (2 runs) a luminous source to induce disability glare, as described in the psychophysical assessment. The participants were presented with the same randomized sequences in balanced pseudorandom luminance conditions (~50% of the participants started the task with the luminance source) to ensure that the results were not influenced by eyestrain. Each run comprised 4 conditions (4 different events) resulting from 3 levels of contrast for the 10 cpd spatial frequency. These levels of contrast simulated those previously determined in the psychophysical task: near threshold, threshold with glare (threshold determined in the presence of glare), near threshold with glare, and 2.5 × glare threshold. Each of these conditions/events was presented 16 times.

Results

An experimental run consisted of 200 trials (20 trials for each contrast level). Each trial comprised a stimulation phase in which the Gabor appeared in the center of the screen during 500 ms, followed by a response/fixation period.

A Weibull function was used to fit to the psychometric data using a maximum likelihood procedure to estimate the contrast increment that would produce 80% correct performance. The threshold contrast and near threshold are obtained, for each run, taking the 50% and 75% points, respectively.

Anatomic Data Processing

Three-dimensional T1-weighted anatomic images underwent brain extraction and intensity normalization. Two high-resolution, anatomic magnetization—prepared, rapid-acquisition gradient echocardiograms were aligned to each other and averaged to improve the signal-to-noise ratio. The resulting anatomic images were then reoriented in relation to the anterior and posterior commissure plane and transformed to the Talairach coordinates. Afterward, the cortex was segmented using a BrainVoyager QX automatic cortex segmentation routine and hand-edited to minimize segmentations errors. The cortical surface was reconstructed at the white-gray matter border and rendered as a smooth 3D surface. The resulting mesh representations of each hemisphere were partially inflated for the polar angle map projection.

Retinotopic Mapping

For each subject, a large region of interest (ROI) that included the entire occipital pole was drawn in each hemisphere in the inflated meshes. Then, after averaging the 3 preprocessed functional scans to determine the cortex mesh time course, we ran the population-receptive, field-fitting BrainVoyager procedure for each hemisphere separately. The visual areas V1, V2, and V3 were manually drawn for each subject in each mesh based on a polar angle map. These ROIs were mapped back into the brain volume space and
used as “masks” to the analysis of the BOLD responses elicited by viewing contrast stimuli, described later.

Functional Data Processing

Functional runs were preprocessed by applying slice scan time correction, linear trend removal, temporal high-pass filtering (2 cycles per run), and 3D interscan head motion correction with cubic spline interpolation. A slight spatial smoothing with a Gaussian filter of 3-mm full-width half maximum and mean intensity adjustment was applied to the functional data acquired under the event-related design paradigm. Because the head motion was minimal, less than 1 voxel (2/3 mm for the block/event-related design, respectively), no runs had to be excluded. Functional scans were aligned to each subject’s structural scan in Talairach space.

Statistical Analysis

Blood Oxygen Level Dependent Signal in the Primary Visual Cortex. Statistical analysis and comparisons were performed on individual and group data. First, to investigate the effect of the glare source in the early visual cortex, we ran a multistudy general linear model (GLM) for each subject separately. Because of the nature of our paradigm (event-related design), we applied a deconvolution analysis that allows estimating the hemodynamic response function for each event type (contrast condition). The averaged BOLD responses were determined in the presence and absence of the glare source, and the mean condition effects (8 beta values) were obtained for each selected ROI.

Exploratory Analysis of Effort-Related Areas. To make comparisons between and within groups (patients and controls), we performed a whole-volume multisubject random effects (RFX) GLM analysis. A 2-way analysis of variance (ANOVA) was conducted to compare patients and controls for each stimulation condition. In this analysis, we compared fMRI runs displaying a difficult visual stimulus with fMRI runs displaying a more visible stimulus. The difficult stimulus was a glare threshold sinusoidal grating surrounded by a glare source (as detailed earlier), and the more visible stimulus was a sinusoidal grating with 2.5× the glare threshold and no surrounding light source.

Questionnaire raw data were Rasch scaled for the 3 subscales (frequency, severity, and bothersome). By using the “bothersome” results, patients were divided into 2 groups (low and high score) on the basis of the median value. We compared high-score patients (feeling more bothered by a visual symptom) with low-score patients when both were presented with a low-contrast stimulus (threshold) under glare. We then performed a whole brain analysis with functional magnetic data from these groups using an RFX group analysis with deconvolution design. The resulting group statistical maps were corrected for multiple comparisons using the false discovery rate at a P value < 0.05.

Relationships among questionnaire scores, total and higher order RMS, MTF, Strehl ratio, and psychophysical contrast thresholds were assessed with Pearson correlation or Spearman’s nonparametric correlation tests, after testing normality with Shapiro–Wilks tests. Other secondary outcomes were compared within groups using t tests or Wilcoxon rank-sum test, as applicable. The significance level adopted was 0.05. SPSS version 23 (SPSS Inc., Chicago, IL) was used for the analyses.

Sample Size

The sample size was selected on the basis of within-group comparisons, taking into account that in fMRI studies even small sample sizes (e.g., n = 10 per group) can achieve power of the order of 80% or 90% if the probabilities of activation in the 2 groups are sufficiently separated (e.g., 15%–20% difference). According to Desmond and Glover, in fMRI studies a minimum of 12 subjects are needed to ensure 80% power at an alpha = 0.05. Because of the variability of the occurrence of dysphotopsia in patients receiving multifocal IOL implants, we decided to study a larger number of these subjects to ascertain as accurately as possible the multifocal IOL outcomes. In both within-group and between-group comparisons, with the exception of the BOLD signal analysis, in which we ran a GLM at the individual level, we conducted an ANOVA with 1 within-subjects and 1 between-subjects factor design after running a multishubject random-effects GLM. The ANOVA analysis takes into account the number of subjects of each group. We also corrected the resultant contrast statistical maps for multiple comparisons using the false discovery rate or the Cluster-level Statistical Threshold Estimator plugin.

Results

Demographics

This prospective study included 60 eyes of 30 patients (16 women) with ages ranging from 49 to 74 years (mean age, 61.03 years; SD, 6.08). The control group included 15 subjects (8 women), age and gender matched (mean age, 61.07 years; SD, 6.96; range, 49–73).

Blood Oxygen Level Dependent Signal Characterization in the Primary Visual Cortex

The BOLD β max (peak value of the hemodynamic response curve BOLD signal after the stimulus is presented) and area under the curve of response profiles in the primary visual cortex were significantly lower under glare in multifocal patients, whereas control subjects experienced no significant decrease in both parameters, indicating that patients were more affected by the light source than were controls. β max decreased from 0.10 (standard error of the mean [SEM] ±0.03) to 0.03 (SEM ±0.04) with glare in patients (P = 0.04 and 0.05 for β2 and β3, respectively, Wilcoxon rank-sum test). In contrast, it decreased from only 0.10 (SEM ±0.03) to 0.08 (SEM ±0.03) in controls without and with glare, respectively. The same was found for the area under the curve, which decreased in patients from 0.20 to 0.04, but remained stable in controls (0.19 without glare and 0.17 with glare). This was an objective measure of the impact of glare at the visual cortical level when subjects viewed threshold contrast stimuli (Fig 1).

Attention Network Activation with Glare in Patients

A whole brain analysis was performed to discover which cortical areas are activated when patients with multifocal IOLs are asked to discriminate a low-contrast stimulus under glare. A “difficult” stimulus, consisting of a sinusoidal grating at stimulus contrast threshold, was compared with a higher contrast stimulus without glare (“less difficult” situation, consisting of a similar stimulus but having 2.5× more contrast). We performed this analysis in patients and controls.

Patients showed significant activation of the attention network involving the frontal, middle frontal, parietal frontal, and postcentral gyrus (multisubject RFX, GLM, deconvolution analysis). There was also activation of the anterior cingulate gyrus. In contrast, controls showed only deactivation of visual areas (occipital lobe and middle occipital gyrus) when viewing the “difficult” stimulus, which is in accordance with the fact that the stimulus was less visible (Fig 2). The statistical maps were
corrected using the Cluster-level Statistical Threshold Estimator plugin at $P < 0.03$.

In addition, we also compared directly which areas were relatively more activated in patients than in controls, when both were presented a difficult stimulus (near threshold contrast). Patients had relatively more activations of the anterior cingulate gyrus, caudate body, middle frontal gyrus, superior parietal lobe, and middle occipital gyrus (Fig 3) than controls, in agreement with the results obtained when analyzing the groups separately (Fig 2). Patients also had relative deactivations of the supramarginal and inferior temporal gyrus (7 and 8 areas in Fig 3, respectively).

### Quality of Vision Questionnaire and Functional Imaging Results

The QoV scores assessing visual symptoms on the basis of their frequency, severity, and bothersomeness for patients and controls are presented in Table 1. By using the “bothersome” outcomes, we compared high-score patients (scoring higher than the median, therefore feeling more bothered by a visual symptom) with low-score patients, when both were presented with a low-contrast stimulus (threshold) under glare. The high-score group had significant activation of the frontal and parietal lobes, cingulate gyrus, and caudate, q (false discovery rate) < 0.05 (Fig 4). This was also true for runs without glare, during which high-score patients had significant activation of Brodmann areas 8, 11, and 46 in the frontal lobe, whereas low-score patients showed no activations in these areas, but only deactivations in the occipital lobe, similar to the control group.

### Contrast Detection Threshold

As expected, patients had significantly higher contrast detection thresholds under glare (average, 13.24; SEM, ±1.33) than without the glare source (average, 9.57; SEM, 0.80; t (29) = −5.26, $P < 0.001$), confirming that the luminous source effectively induced disability glare. The same was true for controls (Wilcoxon signed-ranks test, Z = −3.01, $P = 0.003$).

There were no statistically significant correlations between patients’ contrast detection thresholds (with or without glare) and questionnaire scores (frequency, severity, and bothersomeness), indicating that patients with more quality of vision symptoms did not necessarily have higher contrast detection thresholds.

### Visual Acuity and Optical Properties

Monocular distance refraction showed a mean spherical equivalent of −0.25 D (SD, 0.4) in right eyes and −0.20 D (SD, 0.35) in left eyes. Mean refractive astigmatism was −0.28 D (SD, 0.44) and −0.44 D (SD, 0.39) in right and left eyes, respectively. Visual acuities and wavefront analyses are shown in Table 2.

There was no correlation between optical properties in patients (total RMS, higher order RMS, average MTF, MTF for 10 cpd spatial frequency, and Strehl ratio) and any of the questionnaire scores (frequency, severity, or bothersome), Pearson or Spearman correlations, $P > 0.05$. There was also no correlation between visual acuity results and patients’ questionnaire outcomes. The same was true for the control group.

As expected, patients’ contrast detection thresholds were negatively correlated with average MTF and MTF at 10 cpd, with Pearson correlation coefficients of $r = −0.46$ and $r = −0.43$ and $P$ values of 0.02 and 0.03, respectively. Contrast detection thresholds were positively correlated with total RMS, with a Spearman coefficient of $r = 0.62$, $P = 0.001$ and negatively correlated with the Strehl ratio ($r = −0.51$, $P = 0.007$).

### Discussion

Dysphotopsia is an important cause of dissatisfaction after cataract surgery and remains a limiting factor to the more widespread use of multifocal IOL. Even with the new...
diffractive trifocal IOLs, the reported percentage of severe symptoms is approximately 6%.32

Previous research has shown that dysphotopsia cannot be objectively explained by optical parameters per se, and it is accepted that neuroadaptation may lead to an improvement or resolution of these symptoms in the majority of patients.5,13,32 We confirm the notion of objective versus subjective dissociation, because in this study there was also no correlation between patients’ subjective visual symptoms and optical properties (total RMS, higher order RMS, average MTF, MTF for 10 cpd spatial frequency, and Strehl ratio) or contrast detection thresholds. Contrast detection thresholds were positively correlated with the total RMS, indicating that patients with more aberrations had a higher contrast detection threshold. This is expected, because human visual contrast detection is limited by both neural and optical factors.33

Although there is insufficient consensus on the contribution of neuroadaptation to postsurgical care, there is wide consensus on the need to further understand the process,

Figure 2. Top: When patients are asked to discriminate a threshold stimulus under glare in comparison with a 2.5 higher contrast stimulus without glare, there is activation of cortical areas involved in attention (parietal and frontal lobes) and learning (anterior cingulate gyrus). Bottom: Under the same circumstances, controls show relative deactivations in the occipital lobe, but no significant effort, attention, or learning cortical areas engagement. IOL = intraocular lens.
because neural adaptation to multifocality may vary among patients. The first step to any treatment or effective medical preventive strategy is the knowledge of the disease pathophysiology. Until now, dysphotopsia has been addressed solely on the basis of studies of optic properties and questionnaires, and consequently, its neurobehavioral impact remains unclear.

Functional magnetic resonance imaging is noninvasive and therefore is the adequate technology to study dysphotopsia and associated neuroadaptation in the context of multifocal IOLs.

We measured the impact of a glare source on visual and high-level cortical responses to a low-contrast stimulus in patients who recently received multifocal IOL implants. Threshold contrast stimuli were chosen to impose detection of subtle changes and to reflect everyday vision conditions, because contrast sensitivity is an assay of basic spatial vision. Therefore, evaluating cortical contrast response under a glare source is a suitable strategy to replicate these “real-world” conditions. The stimulus spatial frequency was 10 cpd because intermediate/high spatial frequencies have a dominant ecological role in our representation of the world. The intensity and position of the light source were chosen to induce only disability glare, that is, loss of retinal image contrast as a result of intraocular light scatter, although avoiding discomfort and dazzling glare, which activate nociceptive cortical circuits outside the scope of this study. Disability glare was validated at the psychophysics laboratory and then transferred to the magnetic resonance environment. Because it was impossible to use magnetic components, we developed custom hardware that was MRI compatible. We found out that glare decreases the BOLD signal to a low-contrast visual stimulus in the primary visual cortex. This means that patients are more affected by light sources surrounding a visual target.

The most relevant part of the study, a whole brain analysis, was performed to find out which cortical areas were recruited specifically in operated patients. This is important because vision is determined by how the brain processes incoming retinal input, because vision involves “constructive” perception and not merely the analysis of an optically perfect image. Patients showed significant activations of the attention network (frontal, middle frontal, parietal frontal, and the postcentral gyrus) when asked to discriminate low-contrast stimuli under glare in comparison of subtle changes and to reflect everyday vision conditions, because contrast sensitivity is an assay of basic spatial vision. Therefore, evaluating cortical contrast response under a glare source is a suitable strategy to replicate these “real-world” conditions. The stimulus spatial frequency was 10 cpd because intermediate/high spatial frequencies have a dominant ecological role in our representation of the world. The intensity and position of the light source were chosen to induce only disability glare, that is, loss of retinal image contrast as a result of intraocular light scatter, although avoiding discomfort and dazzling glare, which activate nociceptive cortical circuits outside the scope of this study. Disability glare was validated at the psychophysics laboratory and then transferred to the magnetic resonance environment. Because it was impossible to use magnetic components, we developed custom hardware that was MRI compatible. We found out that glare decreases the BOLD signal to a low-contrast visual stimulus in the primary visual cortex. This means that patients are more affected by light sources surrounding a visual target.

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Table 1. Quality of Vision Questionnaire Scores Obtained for Patients with Multifocal Intraocular Lens Implants at Postoperative Week 3 and for Controls, Assessing Symptoms by their Frequency, Severity, and Bothersomeness

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Patients (n = 30)</th>
<th>Controls (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>45.6, 45</td>
<td>24.5, 25</td>
</tr>
<tr>
<td>Severity</td>
<td>38.6, 39</td>
<td>21.6, 22</td>
</tr>
<tr>
<td>Bothersome</td>
<td>30.7, 34</td>
<td>18.4, 14</td>
</tr>
</tbody>
</table>

QoV = Quality of Vision.
The raw response scores were converted to a 0–100 Rasch scale with higher scores indicating worse quality of vision.

Figure 3. Patients and controls were presented a low-contrast stimulus (near threshold). Cortical areas that were relatively more activated in patients were located in the anterior cingulate gyrus (1), caudate body (2), middle frontal gyrus (3 and 4), superior parietal lobe (5), and middle occipital gyrus (6). Random effects (RFX) group analysis, deconvolution design, with false discovery rate correction at $P < 0.05$. COR = coronal plane; qFDR = $q$ [false discovery rate]; SAG = sagittal; TRA = transverse.
with higher-contrast stimuli without glare, confirming that, under glare, top-down attentional and effort-related networks had to be activated to discriminate the threshold stimuli. This activation was not present in controls, who showed only deactivations in the occipital lobe, likely related to visibility levels. Of note, in the same setting, patients also had increased activity in the anterior cingulate gyrus. The cingulate cortex is involved with conflict monitoring, cognitive control, learning, and memory. The anterior cingulate cortex appears to play a crucial role in initiation, motivation, and goal-directed behaviors, and its activation in patients with recently implanted multifocal lenses possibly reflects the engagement of adaptation mechanisms in response to the presence of a difficult and engaging visual task. These findings are supported by previous research providing evidence that not only low-level (visual cortex) but also high-level brain regions (fusiform gyrus, superior parietal cortex, superior frontal gyrus) reflect visibility of low-level grating stimuli and that changes in functional connectivity reflect perceived stimulus visibility.

We also wanted to know whether patients with more pronounced visual symptoms had different cortical activations at fMRI. Therefore, we divided patients into 2 groups based on the “bothersome score” of the QoV questionnaire. Patients who were more bothered by visual symptoms showed more activity in the top-down attentional network (parietal and frontal lobes, as shown in Fig 3). In addition, they also had increased activity in the cingulate cortex and caudate nucleus. The caudate nucleus is involved in the planning of adaptive behaviors toward the achievement of self-relevant goals. It has been shown that increasing the

Table 2. Patient Optical and Visual Acuity Results at Postoperative Week 3

<table>
<thead>
<tr>
<th>Total RMS [mean (μm) ± SD]</th>
<th>0.42±0.17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher-order RMS [mean (μm) ± SD]</td>
<td>0.16±0.08</td>
</tr>
<tr>
<td>Average MTF height (mean ± SD)</td>
<td>0.31±0.09</td>
</tr>
<tr>
<td>MTF for 10 cpd spatial frequencies (mean ± SD)</td>
<td>0.29±0.14</td>
</tr>
<tr>
<td>Strehl ratio (mean ± SD)</td>
<td>0.07±0.05</td>
</tr>
<tr>
<td>Visual acuity (mean ± SD)</td>
<td></td>
</tr>
<tr>
<td>UCDVA (logMAR)</td>
<td>0.06±0.11</td>
</tr>
<tr>
<td>CDVA (logMAR)</td>
<td>-0.01±0.09</td>
</tr>
<tr>
<td>DCNVA (logRAD)</td>
<td>0.13±0.11</td>
</tr>
<tr>
<td>CNVA (logRAD)</td>
<td>0.05±0.08</td>
</tr>
<tr>
<td>UCNVA (logRAD)</td>
<td>0.08±0.12</td>
</tr>
<tr>
<td>DCIVA (logMAR)</td>
<td>0.30±0.11</td>
</tr>
<tr>
<td>UCIVA (logMAR)</td>
<td>0.20±0.11</td>
</tr>
</tbody>
</table>

CDVA = corrected distance visual acuity; CNVA = corrected near visual acuity; DCIVA = distance-corrected intermediate visual acuity; DCNVA = distance-corrected near visual acuity; logMAR = logarithm of the minimum angle of resolution; logRAD = logarithm of the reading acuity determination; MTF = modulation transfer function; RMS = root mean square; SD = standard deviation; UCDVA = uncorrected distance visual acuity; UCNVA = uncorrected near visual acuity.

Wavefront analysis and visual acuity results obtained for patients at the postoperative week 3. All wavefront data were obtained from right eyes without spectacle correction. Left eye values were similar. Visual acuities were evaluated binocularly.
difficulty of a problem to be solved results in increased activity in the caudate nucleus. This is in accordance with our results, showing that patients more subjectively troubled by visual symptoms had increased activity of cortical areas responsible for solving complex tasks.

Study Strengths and Limitations

The increased activity of cortical areas dedicated to attention (frontal and parietal lobes), to learning and cognitive control (cingulate), and to task planning and solving (caudate) likely represents the beginning of the neuroadaptation process. This process refers to the ability of the brain to reorganize its connections in response to the changing patterns of inputs coming from the environment. Indeed, after cataract surgery, especially with multifocal IOLs, there is a profound change in the visual input, which likely leads to the modification of cortical circuitry to adapt to these changes. Because the purpose of this study was to discover the neural responses associated with dysphotopsia, it was important to have a healthy control group completely adapted to a stable optical system. In addition, because dysphotopsia also may occur with monofocal IOLs, particularly in the early postoperative period, the control group included only subjects with no previous intraocular surgery. This allowed testing the critical difference between a clinical group undergoing adaptation and a control group not undergoing adaptation. Therefore, our findings could represent all IOL adaptation and may not be specific for only multifocal IOLs. It would also be interesting, in the future, to compare adaptation in patients undergoing cataract surgery with monofocal versus multifocal IOL implantation.

These findings should be confirmed in studies with a longer follow-up to allow neuroadaptation to be fully implemented and consequent comparison with early results, in which we would expect to see a decrease in the activation of the aforementioned areas.

In conclusion, this study shows an association between patients’ reported subjective difficulties and fMRI outcomes, independent of optical parameters and psychophysical performance. Understanding the neural impact of photic phenomena at the cortical level will help bridge the gap between optical properties and subjective symptoms, and thus improve prevention and treatment of dysphotopsia.

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Abbreviations and Acronyms:
3D = 3-dimensional; ANOVA = analysis of variance; BOLD = blood oxygen level dependent; cd = candela; cpd = cycles per degree; D = diopters; fMRI = functional magnetic resonance imaging; FOV = field of view; GLM = general linear model; IOL = intraocular lens; MRI = magnetic resonance imaging; MTF = modulation transfer function; QoV = Quality of Vision; RFX = random effects; RMS = root mean square; ROI = region of interest; SD = standard deviation; SEM = standard error of the mean.

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