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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. *Ophthalmology 2017;■:1–10 © 2017 by the American Academy of Ophthalmology*

Multifocal intraocular lenses (IOLs) reduce the need for spectacles at near, intermediate, and distance visual tasks.[1,2] However, some patients report low satisfaction levels despite excellent visual acuity, a condition often described as the "20/20 unhappy patient."[3] Important causes of dissatisfaction with multifocal IOLs represent symptoms collectively referred to as "dysphotopsia."[3–6] Positive dysphotopsia manifestations are most frequently reported (glare, halos, and starbursts), whereas negative dysphotopsia phenomena (shadows, penumbra) are less common.[4,6–8] There is a lack of effective treatments for these subjective symptoms, and thus patients may require IOL explantation in 0.3% to 12% of the cases.[4,6,9,10]

Optical parameters per se do not explain these differences in outcomes because forward light scatter, higher-order aberrations, pupil diameter, and uncorrected visual acuity are similar in patients with and without dysphotic symptoms.[5,11] Even after excluding other causes for decreased quality of vision, such as dry eye, posterior capsule opacification, and retinal disease, there is still no identified correlation between subjective glare and objective parameters of optical quality.[3,5,12] This suggests the involvement of other mechanisms underlying visual symptoms and manifestations, possibly at the neural level.[5] Neuroadaptation, defined as the neural changes induced by the new type of visual experience, is often highlighted as

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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,[13,14] 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.[15] 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 pigmentary retinopathy.[16–19]

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 1-week interval. Surgeries were performed under topical anesthesia through a 2.75-mm clear cornea incision in the steepest meridian. Allegro BioGraph (Wavelight AG, Erlangen, Germany) was used for IOL calculation. After phacoemulsification and aspiration, patients received an Acrysof Restor SN6AD1 IOL (Alcon Surgical, Fort Worth, TX), an apodized hybrid lens combining diffractive and refractive regions with a +3.00 addition.

In addition, 15 subjects were recruited from the general ophthalmology clinic, with the following inclusion criteria: distance-corrected visual acuity ≥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[20]). Intermediate vision was evaluated at 80 cm. All measurements were taken under photopic conditions (80 candela [cd]/m^2).

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 sphericocylindrical 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).[21] The first