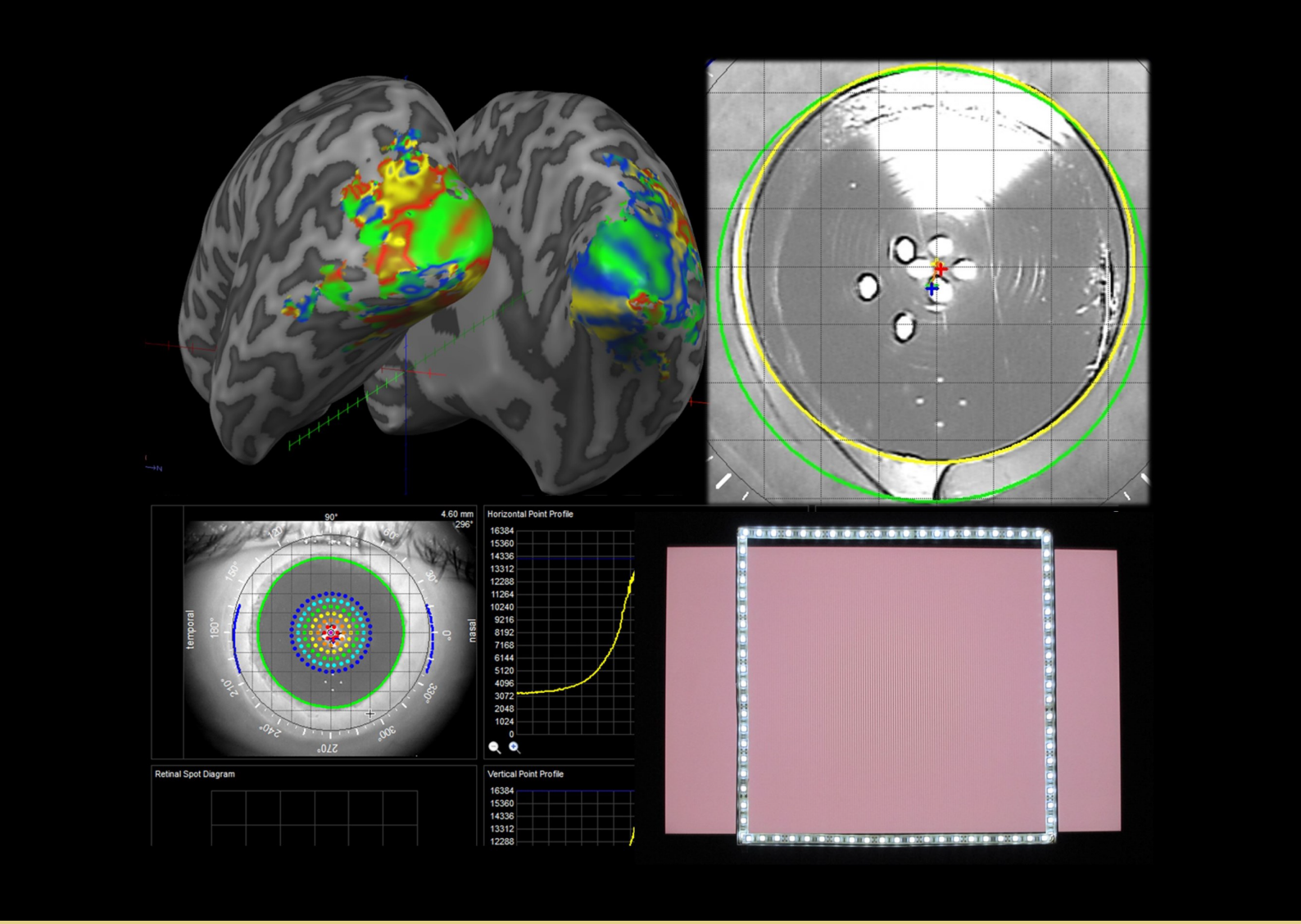

Andreia de Faria Martins Rosa

NEUROADAPTATION AFTER CATARACT AND REFRACTIVE SURGERY

Tese de doutoramento do Programa de Doutoramento em Ciências da Saúde, ramo de Medicina, orientada por Professor Doutor Joaquim Murta, Professor Doutor Miguel Castelo-Branco e Doutora Maria de Fátima Loureiro e apresentada à Faculdade de Medicina da Universidade de Coimbra

Julho de 2017

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Universidade de Coimbra

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Finally, this work would not have been possible without the support of my parents, to whom I dedicate this thesis. They have provided me with the continuous encouragement and love that make all things possible. I am also very thankful to Miqué, for being a great sister and an even better aunt.

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To Alice and Eduardo, my children, for reminding me that asking questions is the way to obtain answers.

TABLE OF CONTENTS

ABSTRACT

Important causes of dissatisfaction after cataract surgery are dysphotopsia (glare, halos, starbursts), requiring intraocular lens (IOL) exchange in 5.7% of cases. Optical parameters *per se* cannot explain why symptoms are different among patients, as no differences have been found in light scatter, aberrations, residual sphere and cylinder. Attempts to link optical outcomes and dysphotopsia have not proven an association between measurable aberrations and symptoms. This suggests the involvement of other mechanisms, possibly at the neural level.

Because these symptoms tend to improve over time, it is thought that the brain adapts to those unwanted stimuli (neuroadaptation). In fact, our vision is determined by how the brain processes incoming retinal input, as vision involves "constructive" perception and not merely the analysis of an optically perfect image. Neuroplasticity is the ability of the brain to reorganize its connections in response to the changing patterns of inputs from the environment.

Functional magnetic resonance imaging (FMRI) has opened an unprecedented opportunity for studying brain activity. We used FMRI to identify changes in neural activity patterns after multifocal IOL implantation over time and their relation with objective and qualitative aspects of visual function.

We enrolled a cohort of patients implanted with multifocal IOLs after cataract surgery and age- and gender-matched healthy controls, without cataract or previous ocular surgery. Patients underwent functional MRI at post-operative intervals of 3 weeks and 6 months. Controls were evaluated at the same time intervals. Functional stimuli consisted in sinusoidal gratings with threshold contrast and a light source to induce disability glare. Subjective quality of vision and reading performance were assessed and wavefront analyses were conducted in both groups.

To set up the experiment we designed a contrast assessment psychophysical task and a functional MRI task, created a proprietary magnetic resonance compatible LED frame with associated dimmer and an innovative psychophysical set up that allows contrast sensitivity evaluation under a glare source. We also developed the Portuguese version of the Radner Reading Tests (Radner-Coimbra Charts) to evaluate reading performance in our patients.

With the first visit data (3rd week) we demonstrated the association between patient reported subjective difficulties and FMRI outcomes, independently of optical parameters and psychophysical performance. The increased activity of cortical areas dedicated to attention

(frontoparietal circuits), learning and cognitive control (cingulate) and to task goals (caudate) likely represented the beginning of the neuroadaptation process to multifocal intraocular lenses.

In addition, we investigated the relation between optical properties, visual function, subjective quality of vision and population receptive fields (PRF). PRF are the aggregate receptive field of the neurons within an FMRI voxel that respond to stimulation of a particular retinal location. Smaller PRFs reflect more fine-tuned visual processing, effectively increasing the spatial resolution of the visual system, while large PRFs reflect a coarser neural representation of visual space. We found that optical properties of the eye influenced PRF sizes. Aberrations of the visual system had a negative influence on visual cortical processing. Moreover, we reported the dissociation between subjective quality of vision and PRF sizes, indicating that patients with better cortical resolution may have improved perception of dysphotic phenomena, and consequently more quality of vision complaints, in spite of the improved optical quality. These findings complement the aforementioned results, concerning the absence of correlation between subjective quality of vision complaints and optical properties.

Finally, using the same set up of the first study visit, we studied all study subjects five months later, to allow comparison between early results and those obtained after neuroadaptation is likely to be fully implemented. Patients no longer showed increased activity of cortical areas involved in visual attention, procedural learning, effortful cognitive control and goal oriented behavior at 6 months. There were no differences between visits in aberrations, Strehl ratio or modulation transfer function. There were significant improvements in questionnaire symptom scores, visual acuity and reading performance. The control group remained unchanged.

In conclusion, our work contributed to identify that neuroadaptation to multifocal IOLS takes place initially through recruitment of visual attentional and procedural learning networks. Thereafter, a form of long-term adaptation/functional plasticity occurs, leading to brain activity regularization towards a non-effort pattern. Our neuroimaging findings are consistent with functional and questionnaire outcomes and are unrelated to optical properties, which reinforce the crucial adaptive role of higher-level brain regions in our perceptual construction of vision. Such information provides background knowledge for the identification of therapeutic targets and of intraocular lens characteristics that are more likely to trigger neuroadaptation circuits effectively and, hence, lead to practical clinical use.

RESUMO

As disfotópsias (brilhos, halos, riscos estrelados) são uma causa importante de insatisfação após cirurgia de catarata, levando à substituição da lente intraocular (IOL) implantada em 5.7% dos casos. Os diversos parâmetros óticos não explicam *per se* as diferenças nas queixas subjetivas dos doentes, já que não são encontradas diferenças em termos de dispersão da luz, aberrações, esfera ou cilindro residuais.

Não existe uma associação clara entre aberrações óticas e sintomas, o que sugere o envolvimento de outros mecanismos, provavelmente a nível neuronal.

Atendendo a que as disfotópsias tendem a melhorar ao longo do tempo, pensa-se que o cérebro se adapta à presença destes estímulos indesejados (neuroadaptação). De facto, a nossa visão é determinada pela forma como o cérebro processa estímulos provenientes da retina, já que a visão envolve uma perceção construtiva e não apenas a receção de uma imagem oticamente perfeita. Neuroplasticidade é, justamente, a capacidade de o cérebro reorganizar as suas conexões em resposta às modificações provenientes do exterior.

A ressonância magnética funcional (FMRI) permite estudar a atividade do cérebro *in vivo*. No presente estudo recorremos à FMRI para identificar modificações nos padrões de atividade neuronal após implante de lentes multifocais, ao longo do tempo, bem como a sua relação com aspetos objetivos e qualitativos de função visual.

Avaliámos uma coorte de doentes submetidos a cirurgia de catarata com implante de lentes multifocais e controlos saudáveis, ajustados à idade e ao género, sem catarata nem antecedentes cirúrgicos oftalmológicos. Os doentes foram submetidos a FMRI 3 semanas e 6 meses após a cirurgia. Os controlos foram examinados nos mesmos intervalos temporais. O estímulo funcional consistiu em riscas sinusoidais com contraste limiar e uma fonte de luz para induzir brilhos. As aberrações óticas, a qualidade de visão subjetiva e o desempenho na leitura foram avaliadas em ambos os grupos.

Para a execução da tarefa experimental procedemos ao desenho das tarefas de FMRI e psicofísica, criámos uma moldura de LED com reóstato compatível com ressonância magnética e um teste psicofísico inovador, que permite determinar o limiar de contraste sob fonte de luz. Desenvolvemos ainda a versão portuguesa do teste de leitura de Radner (Tabelas de Leitura de Radner-Coimbra).

Os resultados obtidos demonstram uma associação entre as dificuldades reportadas pelos doentes e os dados de FMRI, independentemente dos parâmetros óticos. A maior ativação relativa de áreas corticais dedicadas à atenção (circuitos frontoparietais), aprendizagem e controlo cognitivo (córtex cingulado) e aos objetivos da tarefa (caudado) representam provavelmente o início do processo de neuroadaptação às lentes multifocais intra-oculares.

Além disso, investigámos a relação entre propriedades óticas, função visual, qualidade de visão subjetiva e os campos recetores populacionais (PRF). Os PRF são o conjunto dos campos recetores dos neurónios de um voxel de FMRI que respondem à estimulação de determinado local retiniano. Campos mais pequenos refletem um processamento visual mais perfeito, aumentando a resolução espacial do sistema visual, enquanto PRF maiores refletem uma representação neuronal mais grosseira do espaço visual.

Descobrimos que as propriedades óticas do olho influenciam o tamanho dos PRF. As aberrações do sistema visual têm um impacto negativo no processamento visual cortical. Adicionalmente, reportámos a dissociação entre qualidade visual subjetiva e tamanho dos PRF, indicando que doentes com melhor resolução cortical podem ter melhor perceção de fenómenos disfóticos, e, consequentemente, mais queixas no que respeita à qualidade visual, apesar da melhor qualidade ótica. Os resultados do estudo dos PRF complementam assim os achados previamente descritos, sobre a relativa independência entre qualidade de visão subjetiva e propriedades óticas do olho.

Finalmente, usando a mesma metodologia empregue na primeira visita, avaliámos todos os participantes do estudo 5 meses depois, para permitir a comparação entre os resultados iniciais e os obtidos numa altura em que a neuroadaptação já estará implementada. Os doentes apresentam, na segunda visita, uma normalização das áreas ativadas preferencialmente na primeira visita (áreas de atenção, aprendizagem processual, controlo cognitivo e comportamento orientado para os objetivos). Não houve alterações significativas entre visitas no que respeita a aberrações óticas, rácio de Strehl ou função de transferência modular, apesar da melhoria significativa na pontuação dos questionários, acuidade visual e desempenho na leitura. O grupo controlo não apresentou alterações ao longo das visitas.

Em conclusão, este trabalho contribuiu para estabelecer que a neuroadaptação às lentes multifocais intraoculares ocorre inicialmente através do recrutamento de redes neuronais ligadas à atenção e à aprendizagem processual. Estabelece-se uma forma de adaptação a longo prazo/ plasticidade neuronal, levando à normalização da atividade neuronal no sentido de um padrão de não-esforço. Os achados de neuroimagem são consistentes com a desemprenho funcional e com os resultados do questionário, independentemente das

propriedades óticas, o que reforça o papel crucialmente adaptativo das áreas de alto-nível do cérebro na construção percetual da visão.

Os conhecimentos assim obtidos proporcionam as bases para a identificação futura de agentes terapêuticos em casos de não adaptação e das características presentes nas lentes intra-oculares que mais eficazmente possam ativar circuitos de neuroadaptação, levando, assim, à sua aplicação na prática clínica.

INTRODUCTION

Cataract surgery is the most frequently performed surgical procedure in Ophthalmology and is an inevitable consequence of ageing.[1] Presbyopia is the natural decline in near vision that occurs in human healthy aging. Surgical interventions addressing cataract and presbyopia are widely used, such as removal of the cataract/lens with implantation of multifocal intraocular lenses (IOL).[2]

Multifocal IOLs reduce the need for glasses at near, intermediate and distance visual tasks and represent an increasingly important IOL segment.[3] However, some patients are unhappy despite excellent visual acuity. This has been described as the "20/20 unhappy patient".[4] Important causes of dissatisfaction with multifocal IOLs are symptoms collectively referred to as dysphotopsia.[4-7] Positive dysphotopsia manifestations are most frequently reported (glare, halos and starbursts) while negative dysphotopsia phenomena (shadows, penumbra) are rarer.[5, 7-9] These symptoms reflect aspects that go beyond the simple definition of quantity of vision, as expressed by visual acuity, and reflect the more comprehensive notion of quality of vision.

There is a lack of effective treatments for these complaints, leading 4-12% of the cases to require IOL explantation.[5, 7, 10] According to the American Society of Cataract and Refractive Surgery/ European Society of Cataract and Refractive Surgeons 2007 survey update on complications of foldable intraocular lenses, the most common reason for explantation or secondary intervention after multifocal IOLs was glare/optical aberrations (68%).[11] These complications have remained a drawback to the more widespread use of multifocal IOLs.[10, 12]

Attempts to link quantifiable optical outcomes and dysphotopsia have not succeeded in proving a clear association between measurable aberrations and symptoms.[6] There are no differences in forward light scatter, higher-order aberrations, pupil diameter and uncorrected visual acuity between patients with and without visual symptoms, which shows that optical parameters *per se* do not explain these differences.[4, 10] This suggests the involvement of other mechanisms underlying visual complaints and manifestations, possibly at the neural level. Even after excluding other causes for decreased quality of vision, such as dry eye, posterior capsule opacification and retinal disease, there is no correlation between subjective glare and objective parameters of optical quality.[6, 7]

Because these symptoms tend to improve over time in most patients, it is thought that the brain adapts to the new input, which is referred to as neuroadaptation in the literature in this field.[5, 13-18] One way to express it is that two patients may have identical visual outcomes in terms of objective function but very different perception of their quality of vision. In fact, our vision is determined by how the brain processes incoming retinal input, as vision involves "constructive" perception and not merely the analysis of an optically perfect image.[19]

The complexity associated with individual adaptation to changing visual input has been demonstrated for other disorders affecting the anterior segment of the eye.[20] With the same optical quality obtained with adaptive optics, visual performance is significantly worse in keratoconic eyes compared to normal eyes, especially in those with more higher-order aberrations.[20] This is especially relevant as keratoconus is a disease that affects the cornea of young adults, thus excluding amblyopia as the explanation for the lack of improvement of visual acuity. This lack of improvement is attributed to neural factors, i.e., neural insensitivity after the critical period of plasticity because of long-term visual experience with poor retinal image quality.[20] In fact, visual performance is influenced by retinal and neural factors in addition to optical aberrations.[21] Neural adaptation to blur influences visual performance deeply, even in normal eyes.[22] Subjects prefer the blur induced by their own higher-order aberrations in comparison to a rotated version of the same aberrations, indicating that their neural visual system was adapted to the optical properties of the eye.[23]

Neuroplasticity refers to the ability of the brain to reorganize its structural and/or functional connections and/or local organization in response to the changing patterns of inputs coming from the environment.[24] Behavioral manifestations of visual plasticity in humans comprise perceptual learning and adaptation, under the top-down control of attention.[3, 25-27] Perceptual learning is a process in which practicing a challenging task leads to significant and persistent improvements in visual performance.[25-27] Visual adaptation can both refer to changes in neural processing because of repeated brief exposures or because of the maintained presence of a stimulus in the long term.[26, 27] In this case, the causal effects are permanent and long-term structural plasticity is induced. Both short and long-term adaptation can occur because of the presence of blur resulting from the optics of the eye.[27, 28] In addition, adaptation adjustments tend to mask sensitivity losses that appear with disease and with ageing, which implies that the process of adaptation remains largely functional in the senescent visual system.[28-30] Thus, adaptation may be important for matching vision to the optical quality of the eye throughout life.

Functional magnetic resonance imaging (FMRI) has opened an unprecedented opportunity for studying brain activity in vivo and thus to better understand plasticity in the visual cortex. Previous FMRI studies have shown that BOLD (blood oxygenation level dependent) contrast responses within the primary visual cortex are enhanced with increasing stimulus luminance contrast, paving the way for studies of contrast response functions.[31-33] Furthermore, FMRI has also been used to show the presence of neuroplasticity in other eye diseases, such as retinitis pigmentosa, macular degeneration and amblyopia.[24, 34-36]

Therefore, we used functional magnetic resonance imaging to study the process of neuroadaptation in patients equipped with multifocal IOLs at two time points: at the early post-operative period (3rd week) and at the 6th postoperative month.

In each of these visits, subjects were presented with a low-contrast sinusoidal grating while inside the magnetic resonance bore, to measure the corresponding cortical response BOLD signal. The stimulus contrast was determined for each patient (threshold and near threshold) in the laboratory and was used in the FMRI scans in both visits.

We assessed neuroadaptation with three FMRI parameters: visual cortex activation, attention-effort network activation and population receptive fields, as well as with clinical parameters (visual acuity and reading performance), psychophysical tests (contrast detection), optical properties and questionnaire scores.

Thesis outline

This thesis is divided into three parts plus supplements. It comprises four published articles and two manuscripts under review at international peer-reviewed journals.

Part I provides the background information that led to the research question and is based on an original article concerning quality of vision after cataract surgery – *Comparison of visual function after bilateral implantation of inferior sector-shaped near-addition and diffractive-refractive multifocal IOLs.* In this article we compared visual function after bilateral implantation of two different multifocal IOLs and noticed important differences in quality of vision aspects (photopic and mesopic contrast sensitivity), despite similar results in terms of quantity of vision (distance, intermediate and near visual acuities). There were also important differences concerning the impact of a glare source on visual acuity, ranging from 0 to 87% of correctly identified optotypes in the presence of a light source, which led to the question – why are functional outcomes so different when optical results are so similar?

In addition, part I is an overview of the state of the art in the field of plasticity in the adult visual cortex, based on the review article *Plasticity in the Human Visual Cortex: An Ophthalmology-Based Perspective*.

Part II describes the methodology, results of the study, and contains two published original articles and two original manuscripts under review.

The article *Development of the Portuguese version of a standardized reading test: the Radner-Coimbra Charts* focuses on the development of an important tool for quality of vision assessment, as reading has a crucial role in everyday life.

The article *Functional magnetic resonance imaging to assess the neurobehavioral impact of dysphotopsia with multifocal intraocular lenses* shows the results of the patient´s first visit in the research project. Patients recently implanted with multifocal lenses had stronger recruitment of cortical areas involved in learning, task planning and solving. In addition, patients reporting more dysphotopsia showed significantly increased activity in task and effort-related brain regions. There was also dissociation between optical properties and subjective symptoms. This dissociation is further detailed in the original manuscript *Optical properties influence visual cortical resolution after cataract surgery and dissociate from perceived quality of vision.*

The manuscript *Functional magnetic resonance imaging to assess neuroadaptation to multifocal intraocular lenses: a longitudinal study* presents the results of the last visit of the study. It shows that neuroadaptation to multifocal IOLS occurs through a process of attentional network (fronto-parietal) and cingulate recruitment in the initial post-operative period, and that there is an improvement in contrast detection and questionnaire scores, despite the stability of optical properties. It concludes that there is a form of long-term adaptation/ functional plasticity, leading to a regularization of brain activity towards a non-effort pattern at 6 months.

Part III provides an integrated discussion summarizing the main results and contributions of this thesis, while addressing future research in the area.

Competition funded projects

- **Research Grant from the Research Office of the Faculty of Medicine, University of Coimbra**

"Functional brain imaging as an innovative tool for assessing dysphotopsia after cataract surgery". April 2014

- **D.Manuel de Mello 2014 Research Grant**

  First position among proposals from Portuguese doctors (less than 35 years) involved in research at Medical Universities. "Neuroadaptation after Cataract Surgery". November 2014

- **European Society of Cataract and Refractive Surgeons Clinical Research Awards 2015**

  Funding for pilot study of "NEuroadaptation after Cataract and Refractive SUrgery Study – NECSUS study". February 2016.

Publications list

1. **Plasticity in the Human Visual Cortex: an Ophthalmology-Based Perspective**

   Martins Rosa A, Silva MF, Ferreira S, Murta J, Castelo-Branco M

   Biomed Res Int. 2013;2013:568354

2. **Comparison of visual function after bilateral implantation of inferior sector-shaped near-addition and diffractive-refractive multifocal IOLs**

   Rosa AM1, Loureiro Silva MF, Lobo C, Mira JB, Farinha CL, Póvoa JA, Castelo-Branco M, Murta JN

   J Cataract Refract Surg. 2013 Nov;39(11):1653-9

3. **Development of the Portuguese version of a standardized reading test: the Radner-Coimbra Charts**

   Rosa AM, Farinha CL, Radner W, Diendorfer G, Loureiro MF, Murta JN

   Arq Bras Oftalmol. 2016 Jul-Aug;79(4):238-42

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

   Rosa AM, Miranda ÂC, Patrício M3, McAlinden C, Silva FL, Murta JN, Castelo-Branco M.

   Ophthalmology. 2017 Apr 19. pii: S0161-6420(16)32443-5

5. **Functional magnetic resonance imaging to assess neuroadaptation to multifocal intraocular lenses: a longitudinal study**

   Andreia M. Rosa, Ângela C. Miranda, Miguel M. Patrício, Colm McAlinden, Fátima L. Silva, Miguel Castelo-Branco, Joaquim N. Murta

   Under review, Journal of Cataract and Refractive Surgery

6. **Optical properties influence visual cortical functional resolution after cataract surgery and both dissociate from perceived quality of vision**

   Ângela Sofia Cardoso Miranda, Andreia de Faria Martins Rosa, Miguel José Patrício Dias, Ben M. Harvey, Maria Fátima Loureiro da Silva, Miguel de Sá e Sousa Castelo-Branco, Joaquim Carlos Neto Murta

   Under review, Investigative Ophthalmology & Visual Science

PART I

BACKGROUND

We started with a question – how to improve quality of vision? Quality of vision is more than the foveal quantity of vision or visual acuity. It reflects not only the ability to identify black optotypes against a white background, but also contrast sensitivity, dysphotic symptoms presence and mesopic vision. Cataract and refractive surgery today aim at improving visual function in terms of both quantity and quality of vision.

We have been involved in the clinical evaluation of different multifocal intraocular lenses throughout the years. One of these studies compared visual function after cataract surgery with implantation of inferior sector-shaped near-addition versus diffractive-refractive multifocal IOLs. We evaluated visual acuity, glare disability, color vision and contrast sensitivity under photopic and low mesopic conditions. Despite similar refractive and visual acuity results, there were significant differences in contrast sensitivity and glare disability. The diffractive-refractive IOL had better outcomes in terms of photopic contrast sensitivity for intermediate and high spatial frequencies and under mesopic conditions for all spatial frequencies, except for the highest (23.6 cycles per degree). These findings highlight the importance of a complete visual function evaluation in cataract and refractive surgery, especially when new materials and designs are first available for clinical use.

In addition, this study provided intriguing data on the presence of glare disability. The ability to identify optotypes under the influence of a light source ranged from 0% of correct answers to 87%, despite the fact that all patients had at least 20/50 of uncorrected distance visual acuity.

We reported these findings in the original article number 1 of this thesis "Comparison of visual function after bilateral implantation of inferior sector-shaped near-addition and diffractive-refractive multifocal IOLs".

Such differences in quality of vision have been attributed to neuroadaptation, a process by which the brain adapts to the new visual input created by the removal of the crystalline lens and consequent implantation of an IOL. This ability to change reflects some level of plasticity in the adult human brain, contrasting with the classical notion of stability of the human visual cortex after childhood.

To understand current knowledge on the field of plasticity in adults we performed a literature review, which originated the review article "Plasticity in the Human Visual Cortex: An Ophthalmology-Based Perspective".

Both articles are published and can be found in the next pages.

Comparison of visual function after bilateral implantation of inferior sector-shaped near-addition and diffractive-refractive multifocal IOLs – original article number 1

ARTICLE

Comparison of visual function after bilateral implantation of inferior sector-shaped near-addition and diffractive–refractive multifocal IOLs

Andreia Martins Rosa, MD, Maria Fátima Loureiro Silva, PhD, Conceição Lobo, MD, PhD, Joaquim Bernardes Mira, MD, Cláudia Louro Farinha, MD, João Alberto Póvoa, MD, Miguel Castelo-Branco, MD, PhD, Joaquim Neto Murta, MD, PhD

PURPOSE: To compare visual function after bilateral implantation of multifocal Lentis Mplus LS-312 (Group A) or Acrysof Restor SN6AD1 (Group B) intraocular lenses (IOLs).

SETTING: Ophthalmology Unit, Centro Hospitalar e Universitário de Coimbra, and Visual Neuroscience Laboratory, IBILI, Faculty of Medicine, University of Coimbra, Coimbra, Portugal.

DESIGN: Comparative case series.

METHODS: Patients between 49 years and 76 years had bilateral cataract surgery with multifocal IOL implantation. Patients were evaluated preoperatively and 3 months postoperatively for distance, intermediate, and near visual acuities; static photopic and mesopic contrast sensitivity; and visual acuity under a glare source using the Metrovision contrast sensitivity platform. Color vision was evaluated with the Cambridge Colour Test.

RESULTS: Group A comprised 56 eyes and Group B, 44 eyes. Visual and refractive results were comparable between the 2 groups. Photopic contrast sensitivity was significantly better in Group B at intermediate (2.2 cycles per degree [cpd] and 3.4 cpd) and high (7.1 cpd and 23.6 cpd) spatial frequencies. Under low mesopic conditions (0.08 candelas/m^2), differences were significant at 1.1 cpd and 2.2 cpd spatial frequencies. There were no differences in visual acuity under a glare source or in color vision.

CONCLUSIONS: Both IOLs provided good distance, intermediate, and near visual acuities. Visual acuity under a glare source and color vision were similar in the 2 groups. However, photopic and low mesopic contrast sensitivities were better in Group B, particularly for intermediate spatial frequencies, which are important for night driving.

Financial Disclosure: No author has a financial or proprietary interest in any material or method mentioned.

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The design of multifocal intraocular lenses (IOLs) has undergone several modifications to improve distance, intermediate, and near vision.[1] However, unwanted side effects, such as glare, halos, and loss of contrast sensitivity, have also often been reported.[2] Asymmetric IOLs with sector-shaped near-vision zones were developed to reduce these side effects, but recent studies[3–6] found that this asymmetric design may increase optical aberrations and affect ocular optical quality, with a harmful effect on daylight (photopic) contrast sensitivity. However, many patients with multifocal IOLs report halos and glare, especially when driving at night (ie, under low mesopic conditions). In addition, intraocular higher-order aberrations (HOAs) increase with pupil dilation and in low-light conditions. Therefore, it might be expected that differences in contrast sensitivity detected under photopic conditions would persist or increase under mesopic conditions.[7–10]

Contrast sensitivity should therefore be tested under low mesopic conditions (ie, 0.08 candelas [cd]/m^2) instead of the higher luminance value (3.0 cd/m^2) used in most studies.[4,11–14] This low value of luminance (0.08 cd/m^2) is more likely to represent the conditions in which patients have difficulties.[11,13,15] For driving on lit roads, the recommended average road-surface

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luminance in Europe and in the United States varies between 0.3 cd/m^2 and 2.0 cd/m^2.[16] Low mesopic contrast sensitivity is particularly important when evaluating multifocal IOLs because it is known that under low-light conditions, some advantages of specific IOL designs are attenuated by pupil dilation.[13,17]

The purpose of our study was therefore to compare the visual acuity, glare disability, color vision, and contrast sensitivity under photopic and low mesopic conditions between a sector-shaped near-vision zone multifocal IOL and a diffractive–refractive multifocal IOL.

PATIENTS AND METHODS

Patients

This prospective comparative case series included patients who had bilateral cataract surgery with implantation of multifocal IOLs. The study was performed in accordance with the ethical standards of the Declaration of Helsinki. Institutional review board approval was obtained, and patients provided informed consent after receiving an explanation of the possible consequences of participation had been explained.

Exclusion criteria were 1.5 diopters (D) or more of corneal astigmatism, irregular topography, illiteracy, and a history of other ocular comorbidities, such as glaucoma, retinal disease, previous corneal or intraocular surgery, and pupil deformation. The study design was consecutive. Once the patients were selected according to the inclusion and exclusion criteria, patients were implanted sequentially with the Lentis Mplus LS-312 C-loop (Oculentis GmbH) (Group A) or with the Acrysof Restor SN6AD1 IOL (Alcon Laboratories, Inc.) (Group B).

Intraocular Lenses

The Lentis Mplus LS-312 C-loop is a biconvex acrylic refractive 1-piece IOL with a sector-shaped near-vision area with a +3.00 D addition (add) and an aspheric posterior surface. The hydrophilic acrylic copolymer has a hydrophobic surface with ultraviolet light–filtering components. Care was taken to position the salient mark at 6 o'clock.

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The Acrysof Restor SN6AD1 is an apodized hybrid IOL combining diffractive and refractive regions with a +3.00 D add. This IOL has a symmetric biconvex design with negative spherical aberration and a blue light–filtering chromophore.

Surgical Technique

Surgeries were performed using topical anesthesia through a 2.75 mm clear corneal incision in the steepest meridian by 1 of 4 experienced surgeons. The Allegro Biograph device (Wavelight AG) and the SRK/T formula[18] were used for IOL calculation. After phacoemulsification and aspiration of the cortex were performed, the IOLs were implanted in the capsular bag.

Preoperative and Postoperative Evaluations

Before surgery, patients had a complete ophthalmic examination including manifest refraction, slitlamp biomicroscopy, topography (Orbscan II, Bausch & Lomb), dilated fundoscopy, and Goldmann applanation tonometry. Distance visual acuity was evaluated with Snellen charts. Intermediate (70 cm) and near (40 cm) visual acuities were evaluated with the near Early Treatment Diabetic Retinopathy Study chart, with an adjustment for intermediate visual acuity, as previously described.[19] All measurements were taken under photopic conditions (80 cd/m^2). Pupil measurements were recorded with a pupillometer (Metrovision) that induced a near infrared illumination (880 nm) under photopic (100 cd/m^2) and mesopic (1 cd/m^2) conditions.

Contrast sensitivity testing was performed using 2 methods; that is, the Pelli-Robson contrast sensitivity chart (Haag-Streit International) and the Metrovision contrast sensitivity platform (Metrovision MonCv3 system).[20] Pelli-Robson testing was performed under only photopic luminance conditions; the log contrast sensitivity of the last triplet for which 2 letters (2 of 3) were named correctly was used as a scoring rule. Contrast sensitivity evaluation based on the Metrovision platform was performed under photopic (mean luminance 80 cd/m^2) and low mesopic (mean luminance 0.08 cd/m^2) lighting conditions at low (0.6 cycles per degree [cpd] and 1.1 cpd), intermediate (2.2 cpd and 3.4 cpd), and high spatial frequencies (7.1 cpd and 23.6 cpd). Sinusoidal grating parameters (luminance, contrast, and spatial frequency) were computer controlled. The program started with low-contrast gratings. Then, the contrast was progressively increased until the patient could see the shape of the grating. Spatial contrast sensitivity function was calculated using the following equation: Spatial contrast sensitivity function (dB) = 10 log [(Lmax + Lmin)/(Lmax − Lmin)], where Lmin is the minimum luminance of the grating and Lmax is its maximum luminance. Contrast sensitivity testing was performed with the best optical correction for the test distance (2 m). Under low mesopic condition (0.08 cd/m^2), patients wore goggles with 3 log unit filters.

A glare test (Metrovision) simulating night-driving conditions was performed by presenting optotypes of calibrated low luminance over a dark background with a lateral high-luminance light source (5 cd/m^2) at the side of the screen. This test consisted of counting the number of letters the patient correctly identified despite diffusion within the eye. The final score was given as a percentage, with 100% being identification of all letters.

Color vision was evaluated using the Cambridge Colour Test (Cambridge Research Systems), a chromatic contrast sensitivity test used to probe red–green and blue–yellow visual pathways, as previously described.[21,22] The participants viewed a static pattern of circles of various sizes and luminances with superimposed chromatic contrast defining a C; they pressed 1 of 4 buttons to indicate whether the gap was facing up, down, left, or right. The Trivector version was used; in this version, targets differ from the background along 1 of the 3 color confusion lines as follows: protan, deutan, and tritan. This test uses 3 randomly interleaved staircases to dynamically adjust the chromaticity of the target according to the participant's performance. All tests were performed monocularly, with the first tested eye chosen at random. Chromatic thresholds were expressed in Commission Internationale de l'Éclairage 1976 u'v' color space units. High chromatic thresholds relate to low-contrast sensitivity.

Postoperatively, patients were evaluated at 1 day, 1 week, and 1 and 3 months. The postoperative examination at 1 month and 3 months was identical to the preoperative examination but with the addition of near (40 cm) and intermediate (80 cm) visual acuity measurements. Monocular data are presented to limit the influence of neuroadaptation mechanisms that occur after multifocal IOL implantation.[11]

Statistical Analysis

Statistical analysis was performed using SPSS for Windows software (version 19.0, SPSS, Inc.). First, the normality of all data samples was evaluated using the Kolmogorov-Smirnov test. When parametric analysis was possible, an independent-samples Student t test was used to compare data between groups. Otherwise the Mann-Whitney U test was used. The Cohen d test and Wilcoxon signed-rank test (r) were used for the statistical measure of effect size. A statistical power analysis was performed with G*Power software (version 3.1.6, Franz Faul, Kiel University, Kiel, Germany) to test whether conclusions conformed the β error testing and sufficient sample size. All results with a P value less than .05 were considered statistically significant.

RESULTS

The study evaluated 100 eyes of 50 patients with a mean age of 66.2 years ± 0.67 (SD) (range 49 to 76 years). Group A comprised 56 eyes of 16 men and 40 women and Group B, 44 eyes of 12 men and 32 women ($P=.83$, Mann-Whitney U test). Table 1 shows the preoperative data by IOL group. There were no statistically significant between-group differences in age, corrected distance visual acuity (CDVA), sphere, cylinder, mean keratometry, mean corneal astigmatism, contrast and color sensitivity, or glare results. Thus, the groups were matched across these dimensions. The sample size, evaluated with a post hoc power calculation, had a minimum achieved power of 0.84.

Visual Acuity and Refraction

The visual and refractive results were comparable in the 2 groups with no statistically significant differences (Table 2). The mean 3-month postoperative uncorrected distance visual acuity, uncorrected intermediate visual acuity, uncorrected near visual acuity, CDVA, and distance-corrected near visual acuity improved (Table 2).

Contrast Sensitivity

Static Photopic Contrast Sensitivity Pelli-Robson 3-month photopic postoperative contrast sensitivity log scores did not differ between the IOL groups (Mann-Whitney $U = 512.5$, $P=.08$). Concerning photopic contrast sensitivity outcomes of Metrovision testing, both groups had comparable sensitivity at the lowest spatial frequencies (0.6 cpd and 1.1 cpd; Srudent t test, 73 degrees of freedom [$t(73)$] = −0.53, $P=.60$, and

Table 1. Between-group comparison of preoperative patient data.

Parameter	Group A Mean ± SE	Group A Range	Group B Mean ± SE	Group B Range	P Value
Age (y)	66.3 ± 6.1	49, 74	66.9 ± 6.9	49, 76	.66*
CDVA (logMAR)	0.26 ± 0.03	0.00, 1.30	0.26 ± 0.02	0.00, 0.70	.36†
Spherical equivalent (D)	0.16 ± 0.36	−7.50, 3.25	−0.43 ± 0.41	−7.50, 2.75	.30†
Sphere (D)	0.42 ± 0.37	−8.00, 4.00	−0.27 ± 0.40	−7.00, 3.00	.18†
Cylinder (D)	−0.58 ± 0.12	−2.50, 1.00	−0.63 ± 0.12	−1.80, 0.50	.57†
Keratometry (D)	44.00 ± 0.28	40.00, 49.40	44.46 ± 0.24	42.15, 48.30	.22†
Corneal astigmatism (D)	0.66 ± 0.04331	0.10, 1.50	0.61 ± 0.05	0.10, 1.50	.46†
PR CS (log units)	1.50 ± 0.03	0.90, 1.95	1.42 ± 0.04	1.05, 1.95	.09†
Red/green (color units)	73.39 ± 5.07	31.00, 250.50	75.45 ± 9.44	34.50, 292.00	.37†
Blue/yellow (color units)	138.88 ± 7.77	50.00, 322.00	142.00 ± 11.47	49.00, 317.00	.82†
Glare (%)	0.15 ± 0.03	0.00, 0.77	0.09 ± 0.03	0.00, 0.73	.39†

CDVA = corrected distance visual acuity; PR_CS = Pelli-Robson contrast sensitivity; SE = standard error
*Mann Whitney test
†Student t test

Table 2. Between-group comparison of 3-month postoperative visual and refractive outcomes.

Parameter	Group A		Group B		*P* Value*
	Mean ± SE	Range	Mean ± SE	Range	
UDVA (logMAR)	0.07 ± 0.02	−0.08, 0.40	0.07 ± 0.01	0.00, 0.30	.42
UIVA (logMAR)	0.26 ± 0.02	0.00, 0.40	0.26 ± 0.02	0.00, 0.40	.90
UNVA (logMAR)	0.15 ± 0.02	−0.10, 0.40	0.16 ± 0.03	0.00, 0.40	.84
CDVA (logMAR)	−0.01 ± 0.01	−0.08, 0.16	0.00 ± 0.01	−0.08, 0.10	.43
Sphere (D)	0.11 ± 0.16	−1.25, 1.00	0.29 ± 0.14	−0.50, 0.50	.80
Cylinder (D)	−0.14 ± 0.17	−1.00, 0.50	−0.36 ± 0.09	−0.75, 0.25	.30
DCNVA (logMAR)	0.14 ± 0.02	0.00, 0.50	0.15 ± 0.02	0.00, 0.40	.73
Near addition (D)	1.53 ± 0.19	0.00, 2.80	1.55 ± 0.12	0.00, 1.75	.572
Mean corneal astigmatism (D)	0.63 ± 0.07	0.20, 1.10	0.65 ± 0.07		.89
Pupil diameter (mm)					
Photopic (100 cd/m^2)	3.29 ± 0.00	3.27, 3.32	3.29 ± 0.00	0.1, 1.7	.89
Mesopic (1 cd/m^2)	4.06 ± 0.04	3.42, 4.85	4.00 ± 0.05	3.42, 4.73	.38

cd = candelas; CDVA = corrected distance visual acuity; DCNVA = distance-corrected near visual acuity; SE = standard error; UDVA = uncorrected distance visual acuity; UIVA = uncorrected intermediate visual acuity; UNVA = uncorrected near visual acuity
*Student *t* test

$t(73) = -1.31$, $P = .19$, respectively). In contrast, there were statistically significant differences in intermediate (2.2 cpd: $t(73) = -2.59$, $P = .011$; 3.4 cpd: $t(73) = -2.48$, $P = .015$) and 1 high spatial frequency (7.1 cpd: $t(73) = -2.59$, $P = .012$; 23.6 cpd: $t(73) = -1.91$, $P = .06$), with better visual performance under photopic contrast sensitivity in Group B (Figure 1). Analysis of effect size using Cohen *d* showed values between 0.60 and 0.63 (higher for intermediate and high spatial frequencies), meaning that Group B IOLs had a moderate to large effect on improving contrast sensitivity at the spatial frequencies studied.

Static Mesopic Contrast Sensitivity Lower contrast sensitivity values were found under mesopic conditions in both groups. Group B had higher mesopic contrast sensitivity values at all spatial frequencies except the highest (23.6 cpd). Differences were statistically significant for 1 low spatial frequency (1.1 cpd: Mann-Whitney $U = 741$, $P = .046$) and 1 intermediate spatial frequency (2.2 cpd: Mann-Whitney $U = 826.5$, $P = .022$) (Figure 2). Effect size for Mann-Whitney *U* test showed a small effect at a frequency of 1.1 cpd ($r = 0.15$) and a medium effect ($r = 0.30$) at an intermediate spatial frequency of 2.2 cpd.

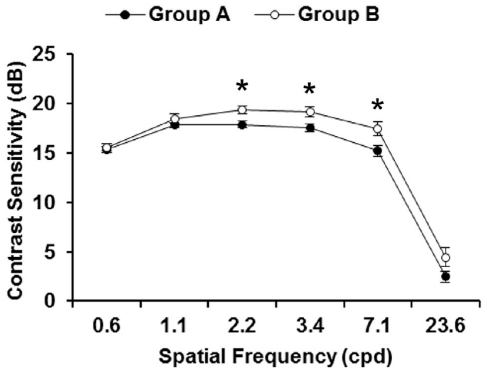

Figure 1. Photopic contrast sensitivity as a function of spatial frequency by group. Error bars represent ±1 standard error of the mean (* = $P < .05$; cpd = cycles per degree).

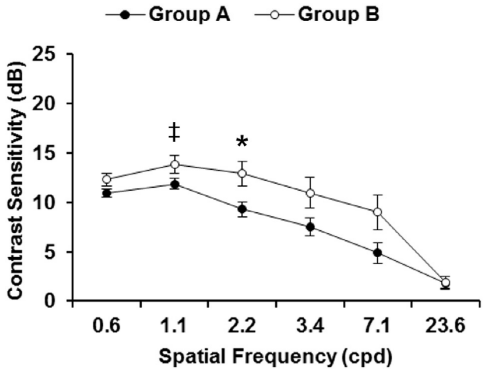

Figure 2. Mesopic contrast sensitivity as a function of spatial frequency by group (‡ = $P = .046$; * = $P = .022$; cpd = cycles per degree).

Chromatic Red–Green and Blue–Yellow Contrast Sensitivity

Red–green values in Group A and Group B were 59.83 ± 4.65 and 58.06 ± 5.45 (u'v' × 10^{-4} color space units), respectively. Blue–yellow values in Group A and Group B were 81.42 ± 4.67 and 86.28 ± 5.59 (u'v' × 10^{-4} color space units), respectively. Between-group comparison of 3-month postoperative color sensitivity outcomes showed no significant differences ($P > .05$, Student t test). Both groups had equivalent color discrimination performance, despite having different light-filtering chromophores.

Glare

There was no significant difference in vision under glare conditions between the 2 groups [$t(73) = 0.51$, $P = .61$]. Group A correctly identified 58% ± 3% (range 0% to 87%) of optotypes, and Group B identified 56% ± 3% (range 23% to 87%).

Complications

There were 3 cases of significant postoperative rotation (> 20 degrees) of the asymmetric IOL. The patients reported blurred vision and difficulty in reading. After surgical repositioning, the symptoms resolved and visual acuity improved. No capsulotomy was required during follow-up.

DISCUSSION

Multifocal IOLs are able to restore distance, intermediate, and near visual acuities.[11,23,24] There is, however, a tradeoff between spectacle independence and visual quality; patients frequently report glare, halos, and a decrease in contrast sensitivity, especially under dim-light conditions.[2,25,26] Efforts have been made to improve IOL design to avoid these symptoms. An asymmetric IOL (Lentis Mplus LS-312), in which an inferior sector is added for near vision, was developed to reduce visual symptoms; light hitting the transition area of the near sector is reflected away from the optical axis.[4] However, because of its asymmetric design with an inferior sector of higher dioptric power, more HOAs, especially primary coma, occur than with several other IOLs.[3–5,12] Because aberrations are known to increase with pupil dilation and under mesopic conditions, it might be expected that differences detected in photopic conditions would persist under mesopic conditions. In addition, in vitro studies[6] comparing the modulation transfer function (MTF) and point-spread function of the Lentis Mplus LS-312 IOL and Acrysof Restor SN6AD1 IOL found better optical quality at distance focus with the diffractive–refractive IOL (Acrysof Restor SN6AD1). Previous studies[12,13] found lower contrast sensitivity with the asymmetric IOL (Mplus LS-312) than with a diffractive–refractive IOL (Acrysof Restor SN6AD1) and with the Mplus LS-312 MF 15 IOL than with an accommodating IOL (Crystalens HD, Bausch & Lomb) under photopic conditions only.

One possible explanation for the apparent contradiction between studies in aberrometry (higher values of HOAs with asymmetric IOLs for a 5.0 mm zone) and contrast sensitivity (no differences under mesopic conditions between IOLs) may be the relatively high levels of luminance (3 cd/m^2) used for creating a mesopic environment.[4,5,11–13,24] Mesopic light levels range from 0.001 to 3.0 cd/m^2.[27] For driving on lit roads, the recommended average road-surface luminances are between 0.3 cd/m^2 and 2.0 cd/m^2 in Europe and between 0.3 cd/m^2 and 1.2 cd/m^2 in the U.S.[16] Luminance levels for evaluating visual performance under night-driving conditions vary between 0.01 cd/m^2 and 1.00 cd/m^2, and night-driving performance deteriorates with decreasing luminance levels from 1.00 to 0.01 cd/m^2.[28] Therefore, luminance values of 3.0 cd/m^2 will not likely reproduce real-world mesopic conditions. We measured mesopic contrast sensitivity under 0.08 cd/m^2, and lower contrast sensitivity was detected with the asymmetric IOL. It is likely that in previous studies, the light conditions (3 cd/m^2) were too bright to detect the deleterious effect of HOAs on contrast sensitivity. In addition, in 1 study,[13] the differences may not have been detected because contrast sensitivity was measured binocularly.

Concerning photopic conditions (80 cd/m^2), we measured lower contrast sensitivity values in the asymmetric IOL group at intermediate spatial frequencies and 1 high spatial frequency, in accordance with previous studies.[12,13] This is expected because the asymmetric IOL induces higher intraocular aberrations and it is known that aberrations have little effect on the transfer factors of very low and very high spatial frequencies.[29] Aberrations mainly reduce transfer factors of intermediate frequencies.[11,12,29]

The performance of the 2 IOLs was similar in the presence of a glare source. Previous studies comparing these IOLs did not evaluate visual acuity under a glare source, despite stating the importance of glare disability with multifocal IOLs. The absence of differences between IOLs despite the improved design (ie, containing only 1 transition zone to reduce sources of scattering and aberrations that cause disturbing reflections, halos, and glare[4]) may be explained by the optical quality provided by the IOLs. In fact, the Group B IOL had higher MTF values than the Group A IOL at all spatial frequencies.[6] Because the MTF shows how an optical system transmits spatial frequencies, lower MTF values mean a loss of information about the details of an object, which decreases image quality and hence visual acuity.[6] The glare test

we used consists of recognizing letters on a screen in the presence of a light source at the side of the screen. Therefore, it is likely to have been influenced by the tradeoff between the optical quality of the IOL and the design, rendering glare results the same across the IOLs.

In terms of color vision, we found no differences in chromatic sensitivity in any of the color pathways studied, despite the presence of a yellow filter in the Group B IOL. The absence of color discrimination differences between clear and yellow IOLs has been reported.[30]

There were 3 cases of IOL rotation in Group A; all required surgical repositioning. This is in accordance with findings in a previous study,[14] in which haptic design was found to be insufficient to provide IOL stabilization.

Near, intermediate, and distance visual acuities were similar in the 2 groups, confirming the usefulness of these IOLs for uncorrected visual acuity. One limitation of this study is the absence of defocus curves. However, this has been extensively reported.[3–5,11–14]

In conclusion, both IOLs provided good distance, intermediate, and near visual acuities. Contrast sensitivity at intermediate spatial frequencies under photopic and mesopic conditions was better in Group B. Lower luminance values for mesopic conditions (0.08 cd/m^2 instead of 3.0 cd/m^2) and glare evaluation are useful in recreating real-world scenarios, such as night driving, thus showing important differences between the IOLs.

WHAT WAS KNOWN

- Photopic contrast sensitivity has been reported to be higher with the Acrysof Restor SN6AD1 IOL than with the Lentis Mplus LS-312 IOL; however, similar outcomes have been found under mesopic light levels of 3 cd/m^2.
- Glare is an important symptom with multifocal IOLs; however, visual acuity under a glare source has not been compared between these 2 IOLS.

WHAT THIS PAPER ADDS

- Contrast sensitivity under low mesopic lighting conditions (0.08 cd/m^2), which is important for night vision, was higher with the Acrysof Restor +3.0 D add IOL.
- Visual acuity under a glare source was similar for the 2 IOLs.

REFERENCES

1. Agresta B, Knorz MC, Kohnen T, Donatti C, Jackson D. Distance and near visual acuity improvement after implantation of multifocal intraocular lenses in cataract patients with presbyopia: a systematic review. J Refract Surg 2012; 28:426–435
2. Woodward MA, Randleman JB, Stulting RD. Dissatisfaction after multifocal intraocular lens implantation. J Cataract Refract Surg 2009; 35:992–997
3. Ramón ML, Piñero DP, Pérez-Cambrodí RJ. Correlation of visual performance with quality of life and intraocular aberrometric profile in patients implanted with rotationally asymmetric multifocal IOLs. J Refract Surg 2012; 28:93–99
4. Alió JL, Piñero DP, Plaza-Puche AB, Rodriguez Chan MJ. Visual outcomes and optical performance of a monofocal intraocular lens and a new-generation multifocal intraocular lens. J Cataract Refract Surg 2011; 37:241–250
5. Alió JL, Plaza-Puche AB, Javaloy J, Ayala MJ. Comparison of the visual and intraocular optical performance of a refractive multifocal IOL with rotational asymmetry and an apodized diffractive multifocal IOL. J Refract Surg 2012; 28:100–105
6. Montés-Micó R, López-Gil N, Pérez-Vives C, Bonaque S, Ferrer-Blasco T. In vitro optical performance of nonrotational symmetric and refractive–diffractive aspheric multifocal intraocular lenses: impact of tilt and decentration. J Cataract Refract Surg 2012; 38:1657–1663
7. Voskresenskaya A, Pozdeyeva N, Pashtaev N, Batkov Y, Treushnicov V, Cherednik V. Initial results of trifocal diffractive IOL implantation. Graefes Arch Clin Exp Ophthalmol 2010; 248:1299–1306
8. Muñoz G, Albarrán-Diego C, Cerviño A, Ferrer-Blasco T, García-Lázaro S. Visual and optical performance with the Re-Zoom multifocal intraocular lens. Eur J Ophthalmol 2012; 22:356–362
9. Yamaguchi T, Negishi K, Ohnuma K, Tsubota K. Correlation between contrast sensitivity and higher-order aberration based on pupil diameter after cataract surgery. Clin Ophthalmol 2011; 5: 1701–1707. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3245194/pdf/opth-5-1701.pdf. Accessed August 10, 2013
10. Wang Y, Zhao K, Yang X, He J, Wang W. Higher order aberrations and low contrast vision function in myopic eyes (−3.00 to −6.00 D) under mesopic conditions. J Refract Surg 2011; 27:127–134
11. Alio JL, Plaza-Puche AB, Javaloy J, Ayala MJ, Moreno LJ, Piñero DP. Comparison of a new refractive multifocal intraocular lens with an inferior segmental near add and a diffractive multifocal intraocular lens. Ophthalmology 2012; 119:555–563
12. Alió JL, Plaza-Puche AB, Montalban R, Javaloy J. Visual outcomes with a single-optic accommodating intraocular lens and a low-addition-power rotational asymmetric multifocal intraocular lens. J Cataract Refract Surg 2012; 38:978–985
13. Alfonso JF, Fernández-Vega L, Blázquez JI, Montés-Micó R. Visual function comparison of 2 aspheric multifocal intraocular lenses. J Cataract Refract Surg 2012; 38:242–248
14. Alió JL, Plaza-Puche AB, Piñero DP. Rotationally asymmetric multifocal IOL implantation with and without capsular tension ring: refractive and visual outcomes and intraocular optical performance. J Refract Surg 2012; 28:253–258
15. Vingolo EM, Grenga P, Iacobelli L, Grenga R. Visual acuity and contrast sensitivity; AcrySof ReSTOR apodized diffractive versus AcrySof SA60AT monofocal intraocular lenses. J Cataract Refract Surg 2007; 33:1244–1247
16. Viikari M, Ekrias A, Eloholma M, Halonen L. Modeling spectral sensitivity at low light levels based on mesopic visual performance. Clin Ophthalmol 2008; 2:173–185. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2698685/pdf/co-2-173.pdf. Accessed August 10, 2013
17. Kurz S, Krummenauer F, Thieme H, Dick HB. Contrast sensitivity after implantation of a spherical versus an aspherical

intraocular lens in biaxial microincision cataract surgery. J Cataract Refract Surg 2007; 33:393–400
18. Retzlaff JA, Sanders DR, Kraff MC. Development of the SRK/T intraocular lens implant power calculation formula. J Cataract Refract Surg 1990; 16:333–340; correction, 528
19. Cuq C, Spera C, Laurendeau C, Lafuma A, Berdeaux G. Intermediate visual acuity without spectacles following bilateral ReSTOR implantation. Eur J Ophthalmol 2008; 18:733–738
20. Baradaran-Rafii A, Eslani M, Sadoughi M-M, Esfandiari H, Karimian F. Anwar versus Melles deep anterior lamellar keratoplasty for keratoconus; a prospective randomized clinical trial. Ophthalmology 2013; 120:252–259
21. Castelo-Branco M, Faria P, Forjaz V, Kozak LR, Azevedo H. Simultaneous comparison of relative damage to chromatic pathways in ocular hypertension and glaucoma: correlation with clinical measures. Invest Ophthalmol Vis Sci 2004; 45:499–505. Available at: http://www.iovs.org/content/45/2/499.full.pdf. Accessed August 10, 2013
22. Silva MF, Faria P, Regateiro FS, Forjaz V, Januário C, Freire A, Castelo-Branco M. Independent patterns of damage within magno-, parvo- and koniocellular pathways in Parkinson's disease. Brain 2005; 128:2260–2271. Available at: http://brain.oxfordjournals.org/content/128/10/2260.full.pdf. Accessed August 10, 2013
23. Javitt JC, Steinert RF. Cataract extraction with multifocal intraocular lens implantation; a multinational clinical trial evaluating clinical, functional, and quality-of-life outcomes. Ophthalmology 2000; 107:2040–2048
24. Alfonso JF, Fernández-Vega L, Puchades C, Montés-Micó R. Intermediate visual function with different multifocal intraocular lens models. J Cataract Refract Surg 2010; 36:733–739
25. Pieh S, Lackner B, Hanselmayer G, Zöhrer R, Sticker M, Weghaupt H, Fercher A, Skorpik C. Halo size under distance and near conditions in refractive multifocal intraocular lenses. Br J Ophthalmol 2001; 85:816–821. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1724058/pdf/v085p00816.pdf. Accessed August 10, 2013
26. Calladine D, Evans JR, Shah S, Leyland M. Multifocal versus monofocal intraocular lenses after cataract extraction. Cochrane Database Syst Rev 2012 issue 9, Art. No. CD003169. Summary available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003169.pub3/pdf/abstract. Accessed August 10, 2013
27. Rea MS, ed, The IESNA Lighting Handbook: Reference & Application, 8th ed. New York, New York, Illuminating Engineering Society of North America, 1993; 27–28
28. Eloholma M, Ketomäki J, Orreveteläinen P, Halonen L. Visual performance in night-time driving conditions. Ophthalmic Physiol Opt 2006; 26:254–263
29. Thall EH, Miller D. Perspectives on aberrations of the eye. In: Yanoff M, Duker JS, eds, Ophthalmology, 3rd ed. St. Louis, MO, Mosby Elsevier, 2009 chapter 2.11
30. Rodríguez-Galietero A, Montés-Micó R, Muñoz G, Albarrán-Diego C. Comparison of contrast sensitivity and color discrimination after clear and yellow intraocular lens implantation. J Cataract Refract Surg 2005; 9:1736–1740

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Review Article

Plasticity in the Human Visual Cortex: An Ophthalmology-Based Perspective

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Neuroplasticity refers to the ability of the brain to reorganize the function and structure of its connections in response to changes in the environment. Adult human visual cortex shows several manifestations of plasticity, such as perceptual learning and adaptation, working under the top-down influence of attention. Plasticity results from the interplay of several mechanisms, including the GABAergic system, epigenetic factors, mitochondrial activity, and structural remodeling of synaptic connectivity. There is also a downside of plasticity, that is, maladaptive plasticity, in which there are behavioral losses resulting from plasticity changes in the human brain. Understanding plasticity mechanisms could have major implications in the diagnosis and treatment of ocular diseases, such as retinal disorders, cataract and refractive surgery, amblyopia, and in the evaluation of surgical materials and techniques. Furthermore, eliciting plasticity could open new perspectives in the development of strategies that trigger plasticity for better medical and surgical outcomes.

1. Introduction

Attempts to improve visual acuity and quality of vision have included advances in visual outcomes evaluation, imaging techniques, and surgical techniques. However, even if we had the perfect method to correct the optics of the eye, our vision would still be determined by the retina-brain interaction. Vision involves perception and not only an optically perfect image. Neuroplasticity refers to the ability of the brain to reorganize the structure and function of its connections in response to the changing environment [1]. It is considered that the brain is plastic and neural networks are initially shaped by experience during the sensitive period and subsequently stabilized during normal development [2]. However, there is growing evidence that visual plasticity occurs not only during childhood, as traditionally considered, but also during all stages of life in response to changes in sensory experience [1]. Functional magnetic resonance imaging (fMRI) has opened an unprecedented opportunity for studying brain activity *in vivo* and thus for better understanding plasticity in the visual cortex [3]. Other methodologies, such as psychophysics and in particular electroencephalography (EEG) and transcranial magnetic stimulation (TMS) may also offer the opportunity to investigate human brain functioning and plasticity. However, because it combines noninvasiveness with high spatial resolution, MRI has become the preferred imaging technique for the characterization of spatial-function relations occurring in plasticity-driven processes [4]. Moreover, if combined with psychophysics, it is a very powerful tool. The focus on pharmacology is also justified by the substantial amount of research on molecular mechanisms and how they can be tackled by pharmacological approaches.

Plasticity can have major implications in the treatment of ocular and cerebral diseases and in the evaluation of materials and surgical techniques (including refractive surgery, cataract surgery, and presbyopia correction). Furthermore, in rodent

models, plasticity can be elicited by reducing intracortical inhibition through pharmacologic treatment with antidepressants, which opens new perspectives in developing therapeutic strategies that harness plasticity for better outcomes [5].

This review focuses on the visual plasticity in the adult human cortex and its role on several ophthalmologic problems. We have organized this review in four major questions in order to answer a main question: Can visual plasticity be used in the future as a tool to correct ophthalmologic problems? The four major questions are as follows. (1) Does visual plasticity occur in adults? (2) What forms of visual plasticity exist in the human cortex? (3) What is the biological background of visual plasticity? (4) What is the relevance of visual plasticity for ophthalmology?

2. Question 1: Does Visual Plasticity Occur in Adults?

Neuroplasticity can be thought as the subtle but orchestrated dance between the brain and the environment [1]. It is the ability of the brain to be shaped by experience and, in turn, for this newly rewired brain to facilitate the embracing of new experiences [1]. Although plastic changes in the brain can occur at any time point in the life cycle, they occur with varying degrees of success [5]. It is known that an abnormal visual experience early in life, usually caused by strabismus, anisometropia, or congenital cataracts, causes amblyopia, an unilateral reduction of best corrected visual acuity that persists during the patient's life [5]. The explanation for these findings is that there are transient connections that go through a process of Hebbian competition in which stronger input signals are favoured and unused connections are pruned permanently [6]. In other words, Hebbian competition works during normal early development to tune the connections to visual cortical neurons, eliminating noneffi-cient inputs and balancing the input from the two eyes [6]. fMRI has shown that visual dysfunctions in amblyopia occur both within and beyond primary visual cortex (V1) including extrastriate and later specialized cortical areas (V4+/V8, lateral occipital complex) [5]. The connectivity of geniculate-striate and striate-extrastriate networks is reduced, and both feedforward and feedback interactions are affected equally [7]. This is in apparent agreement with the traditional view in which the visual system is assumed to be hard-wired long before adolescence.

However, it has been shown that visual acuity can be improved in amblyopic adults through practicing a perceptual learning task (repeating a demanding visual task, such as contrast detection, to improve performance) [8–11]. The improvement of visual function persisted after treatment, showing that the learning was more than a temporary adaptation, thus providing evidence for cortical plasticity in human adults [8–11]. Improvement of visual function after a perceptual learning task was also demonstrated in participants with normal or corrected to normal visual acuity [12]. Plasticity has also been recently demonstrated following retinal ganglion cell functional and structural loss in carriers of a Leber's hereditary optic neuropathy mutation [13].

Video game playing with the amblyopic eye has also been shown to induce cortical plasticity and improve spatial vision in amblyopic adults [14], providing further evidence of plasticity in the adult visual system.

It is likely that some cortical connections are inhibited rather than pruned and that, for some visual functions, there is visual plasticity in adolescence and adulthood [1]. These functionally dormant connections appear to provide the substrate for rapid readaptation in adulthood [15]. For example, there are reports of improved vision in an adult's amblyopic eye after vision in the fellow good eye was lost, with changes occurring so rapidly in some cases that new connections are unlikely to have formed [6].

Scholz et al. in a study involving juggling, a complex motor skill requiring visuo-motor integration, found an increase in dorsomedial occipital gray matter density, likely corresponding to functional visual areas V3A and area V7 [16]. Because activity in this area is implicated in visuospatial imagery, the mentioned changes were attributed to the visualization of the movements and ball trajectories involved in juggling. This study provides evidence for training related structural changes in healthy adult human brain, and, more specifically, in a visual area.

Thus, plastic changes have been seen in the adult human cortex not only in association with overt lesions but also in healthy individuals as a function of experience and training [17]. There is also evidence of a relation in old age between regional cortical shrinkage and increased task-related activation in neuroimaging, suggesting that losses in regional brain integrity drive functional reorganization that compensates/masks cognitive losses from the atrophy [17].

In conclusion, the majority of studies point to the existence of plasticity in adult human visual cortex in response to visual loss in one or both eyes, and there is also a role for visual cortical plasticity in the absence of visual loss.

3. Question 2: What Manifestations of Visual Plasticity Exist in the Human Visual Cortex?

Functional MRI studies have shown that perceptual learning and voluntary attention can bias visual selection and modulate neuronal response in human adult visual cortex [18]. Adaptation is a form of rapid plasticity and leads to strong perceptual effects. By enhancing the visual processing of relevant information and reducing processing of ignored or redundant stimuli, learning, attention, and adaptation shape the landscape of our visual experiences [18].

3.1. Perceptual Learning. A behavioural manifestation of plasticity in humans is the perceptual learning, a process in which practicing a challenging task repeatedly leads to significant and persistent improvements in visual performance over time [15]. The effects of perceptual learning have been well documented beyond the critical period of development in visually normal adults [5]. It has been reported that perceptual learning elicits plastic changes in the visual system,

as shown by changes in V1 activation during fMRI [5]. To evaluate this form of plasticity, neural activity has been measured after participants were intensively trained in a visual task, such as texture discrimination and detecting stimuli orientation [19]. Retinotopic increase in blood oxygenation level-dependent signal (BOLD) response after learning provides empirical support that learning favours activity in the visual cortex in order to increase the discrimination of trained targets from background flankers [20]. The improvement that has occurred in adults as well as in juveniles is specific to the trained eye and develops only across multiple days of training [15]. Training can improve the discrimination of small differences in the offset of two lines (Vernier acuity) and the ability to discriminate orientation, segregate elements of the visual scene, and detect small differences in the depth of two targets [21]. The recruitment of larger assemblies of interconnected neurons or sharpening of cell sensitivity to relevant features of the trained stimulus may produce a higher total neural response associated with increased regionally specific BOLD response [19, 22]. Perceptual learning in the visual system appears to be mediated primarily by changes in the response strength or the tuning of individual neurons, rather than large-scale spatial reorganization of the cortical network as found in the auditory and somatosensory systems [15].

More recently, in line with the benefits of perceptual learning, video games have been shown to improve perception, visuomotor coordination, spatial cognition, and attention, illustrating how an action game play can reshape the adult brain [2, 23]. These plastic changes have been shown to be long lasting, remaining even 2 years after the end of intervention [23]. Action game play primarily targets top-down, attentional systems, possibly altering the excitatory/inhibition balance to allow heightened plasticity [23]. Indeed, it has been shown that complex stimuli are typically not presented at a single retinal location, so their learning is nonspecific to retinal locations and does therefore occur in higher brain areas [12, 24]. Top-down projections from the frontal eye field to visual area V4 can enhance stimulus-related activity, which emphasizes the importance of high level mechanisms [21, 25].

However, the existence of intrinsic plasticity in V1 is controversial, as revealed by difficulties in identifying low-level processes that are context independent, truly local, and not the indirect result of higher level modulation [26, 27]. Additionally, there is increasing evidence for generalization of perceptual learning in conditions previously shown to be specific, such as the training of a different task at a different location allowing the transfer of the feature learning to the second location [12, 28]. This suggests that perceptual learning does indeed involve higher nonretinotopic brain areas that enable location transfer [12, 28]. Not only the retinotopic early visual cortex, but also the nonretinotopic higher brain areas are involved in visual discrimination [29, 30]. Thus, visual perceptual learning seems to involve more than the visual cortex; that is, it involves nonretinotopic higher brain areas, engaged in attention and decision-making [12, 29, 30].

3.2. Attention. Perceptual learning shows a strong interaction with attention, indicating that it is under top-down control [21]. Attention is necessary for the consolidation of memory and virtually all other forms of learning. One of the consequences of learning is to release performance from attentional control, leading to an automatization of the task [21, 31, 32]. Therefore, it is important to consider the influence of attention when evaluating manifestations of visual plasticity such as perceptual learning.

When processing a visual scene, there are mechanisms for selecting relevant and filtering out irrelevant information [33]. This function is accomplished by the attentional system. Two basic sources determine attentional processing: attention driven by the saliency of a signal (bottom-up) and intentions of the observer, mostly directed by task demands, that guide the focus of attention (top-down) [33]. Although these top-down influences originate in the frontal lobe, they primarily modulate neural activation in striate and extrastriate visual areas [33]. fMRI studies have shown that attention can enhance the fMRI signal at early stages of visual processing, including the primary visual cortex [34]. Spatial attention seems not only to enhance processing at attended locations but also to suppress processing at nonattended locations [35]. When more attentional capacity is allocated at central fixation, there is a reduction of cortical activation for task irrelevant peripheral stimuli [36]. The attentional effect increases from V1 to V4, along the hierarchy of visual areas [37]. Top-down signals related to spatially directed attention may be generated by a network of areas in frontal and parietal cortices [38]. Sensory activity in the brain is modulated by attention, memory, and even the intention to act [39]. As an example, in experiences with monkeys, the baseline firing rate of neurons in lateral intraparietal area increases when the animal is working in a task in which it expects that a relevant visuospatial stimulus will appear [39]. Likewise, imaging studies have shown that attention modulates visual responsivity in the human brain [39]. The visual system modifies the retinal image so as to maximize its usefulness to the subject, often originating nonveridical percepts [40]. The visual system does not provide a copy of the external visual world; in contrast, it optimizes processing resources. Attention is an example of this perceptual optimization [41]. Visual attentional load also influences plasticity in the human motor cortex, suggesting that the top-down influence of attention on plasticity is a general feature of the adult human brain [42]. In sum, attention acts upon sensory signals at many levels to construct a selective representation of visual space [39].

3.3. Adaptation. Looking at a pattern for a short time typically decreases sensitivity to that pattern and results in a bias in the appearance of other patterns [43]. Ordinary visual adaptation is considered to occur with brief exposures and their consequent aftereffects [44, 45]. We will refer to the ordinary adaptation as short-term adaptation. However, a process of long-term adaptation can also be found. In this case, a causal effect may be permanent, and the changes

may be given by the structural plasticity following learning processes.

In short-term adaptation, there are changes in sensitivity over short time intervals, ranging from milliseconds to minutes [43]. A classic example is light adaptation. Changes occur so rapidly that structural plasticity is not able to explain it. In long-term adaptation, there are sensitivity adjustments that occur during much longer times, from hours to weeks or even years [43]. These long-term adjustments have been described for color vision, contrast sensitivity, and perceived distortion (blur) [45–47]. For example, when the senescent crystalline lens is removed in cataract surgery, the changes in color appearance follow a very long time course and are not entirely normal even months after surgery [43]. Adaptation has also been shown to occur in natural visual environment, to stimuli that reflect the type of images that observers encounter in everyday viewing [43]. Many aspects of natural vision are routinely regulated by adaptation. Thus, the way we perceive colors, faces, and scenes is strongly dependent on the specific environments we are adapted to [43]. Adaptation also occurs when there are changes in the observer, rather than in the environment, because of eye injury, cataract surgery, or simply a new pair of glasses. For example, adaptation to long-term defocus (myopia and hyperopia) leads to improvements in visual acuity [48].

However, the relationship between adaptation and learning is not entirely clear. The visual system has a large variety of adjustments, and it is difficult to define adaptation in a way that it can be clearly distinguished from other forms of plasticity [43].

Perceptual learning usually produces improvements in discrimination, whereas adaptation is a more immediate loss in sensitivity after exposure to a stimulus [49–51]. Learning can be distinguished from adaptation because it mainly reflects changes in performance rather than in appearance and facilitation instead of suppression. It has a longer time course and changes how the visual system interprets neural signs and not the strength of those signals [51].

Like adaptation, learning can also change the appearance of patterns, and like learning, adaptation can facilitate some discriminations [43]. In fact, the process of adaptation itself might contain forms of learning [45]. With prolonged experience, adaptation is transferred to a long-term memory that can be instantly engaged or disengaged, leaving no aftereffects (the existence of an aftereffect is thought to indicate the presence of an adaptation process or a transient recalibration process) [45]. Both short- and long-term adaptation can occur from the blur resulting from the optics of the eye, including low- and high-order aberrations [52]. In addition, compensatory adjustments of adaptation tend to mask sensitivity losses that appear with disease, so that observers may not be aware of developing visual impairment [43]. Similarly, compensation for age related losses implies that the process of adaptation remains largely functional in the senescent visual system [43, 53, 54]. Thus, adaptation may be important for matching vision to the optical quality of the eye throughout life.

In conclusion, the manifestations of visual plasticity in the human visual cortex include perceptual learning and adaptation, under the influence of attention for resource optimization. These mechanisms are important not only to improve the treatment of ophthalmic disorders but also to understand the crosstalk between the optical system and the brain.

4. Question 3: What Is the Biological Background of Neuroplasticity?

Two types of neuroplasticity can be distinguished, although their frontiers are not well defined: structural plasticity and synaptic or functional plasticity. Synaptic plasticity refers to changes in synaptic activity, leading to changes in synaptic efficacy and in behaviour [55]. Structural plasticity refers to changes in neuronal morphology (axons, dendrites, and dendritic spines), suppression and creation of synapses, and genesis of new neurons and neurites.

Repetitive electrical stimulation of animal nerve fibers can induce an immediate and prolonged increase in synaptic transmission. This effect is called long-term potentiation (LTP) [56, 57]. In contrast, low-frequency stimulation typically induces long-term depression (LTD). These synaptic mechanisms play a role in many forms of learning and memory as well as neuronal development and circuit reorganization [57].

4.1. Physiological Mechanisms That Regulate Developmental Plasticity in the Visual System. Despite the fact that most of the mechanisms referred in the following paragraphs are active during the early phases of visual system development, we have included them in this review since some of them are being increasingly recognized as potential sources of plasticity reinstatement in the adult visual cortex.

The experience-dependent maturation of GABA-mediated inhibition during development establishes the beginning of the critical period for plasticity in the visual system [58]. After monocular deprivation during early life in transgenic animals lacking one isoform of GABA, no variation of visual cortex responsiveness was observed [59]. Therefore, a reduction of inhibitory transmission in early life halts the onset of the critical period for visual cortex plasticity [58]. The limited plasticity in the adult visual cortex can be enhanced by previous visual deprivation, which is associated with a loss of GABA receptors, and reduced by GABAergic modulators [60]. It has been shown that a brief reduction of GABAergic inhibition in the brains of rats is able to reopen a window of plasticity in the visual system a long time after the normal closure of the critical periods [5].

The effects caused by early sensory experience in the remodeling of visual cortical circuitries are preserved throughout life by the appearance of molecular factors in the extracellular milieu that restrict plasticity [61]. The establishment of neuronal connectivity may be, at least in part, under control of structural factors such as myelin-associated proteins (NgR, PirB) and chondroitin sulphate proteoglycans (CSPGs), which all are inhibitory for axonal sprouting [62].

Other important players are the major modulatory systems in the brain, that is, adrenaline, noradrenaline, dopamine, acetylcholine, and serotonin. The adrenergic system has a significant impact on plasticity [57]. Similarly, a single dose of the serotonin reuptake inhibitor citalopram enhances and prolongs plasticity [57]. Calcium channel blockade by nimodipine and dopamine receptor blockade by sulpiride or haloperidol diminish a form of plasticity [57]. Likewise, in the face of compromised cholinergic input to the visual cortex of rats, the ability to perform fine discriminations is impaired, whereas the ability to perform previously learned discrimination remains unaffected, which suggests that acetylcholine facilitates plastic changes in the sensory cortices [63, 64]. Functionally, acetylcholine contributes to plasticity in V1 and is involved in the alteration of tuning properties and map organization in other areas of cortex [64]. Global dopaminergic activation has heterogeneous effects on plasticity. A certain amount of activity of the dopaminergic system is necessary for the induction of plasticity. However, higher dopaminergic activity results in nonlinear effects on plasticity, depending on the dosage, the plasticity induction protocol, and the balance of D1 versus D2 receptor activation [57]. These mediators regulate complex functions of the central nervous system such as different forms of brain plasticity, cognitive processes, and behavior [62].

4.2. Functional Plasticity in the Visual Cortex

4.2.1. Epigenetic Mechanisms of Plasticity, Short Noncoding mRNAs, and the Regulation of Plasticity. Growing experimental evidence indicates that chromatin structure is highly dynamic within the nervous system and that it is recruited as a target of plasticity-associated signal transduction pathways [62, 65, 66]. These mechanisms seem to be important also in the mature system, as increasing acetylation of histones by treatment with histone deacetylase inhibitors effectively reactivates plasticity in the adult visual system [67, 68].

Another mechanism involves CREB (a transcription factor) activity. CREB activity is induced following monocular deprivation in juveniles and declines with maturation of the visual cortex [69].

In addition to the function of transcription factors and modifications of chromatin structure, growing experimental evidence supports a critical role for short noncoding RNAs (microRNAs) which interact with and control translation of mRNA targets, in the regulation of gene expression patterns at the basis of plastic phenomena in the mammalian nervous system [70].

Experience-dependent brain plasticity is consolidated by sleep. This effect may be mediated through the phosphorylation of protein synthesis regulators and the translation of key plasticity-related mRNAs [71]. Sleep promotes cortical mRNA translation, and interruption of this process prevents the consolidation of a form of cortical plasticity *in vivo* [71]. This way, although experience is required for the transcription of key plasticity-related mRNAs, their translation into protein requires sleep, which may represent a sleep-dependent mechanism that converts labile plastic changes into more permanent forms [71].

4.2.2. Mitochondrial Organization-Movement-Activity and Synaptic Activity. The brain can perceive, detect, discriminate, and recognize consciously only those pieces of information which reach a critical level, which can be at least indirectly related to bioenergetics and neuronal mitochondrial activity [72]. Representation of various sensory information can become conscious in our minds only if it reaches a threshold level of energy and duration [72].

Neurotransmitters dopamine and serotonin (which regulate different forms of brain plasticity, as explained previously) can reversibly control mitochondrial motility and distribution. Dopamine displays a net inhibitory effect on mitochondrial movement, but serotonin has a stimulatory effect [72]. There is a direct coupling between mitochondrial organization-movement-activity and synaptic activity [73].

Extension or movement of mitochondria into dendritic axons that are located far from the cell protrusions correlates with the development and morphological plasticity of dendritic spines [74, 75]. Molecular manipulations that reduce dendritic mitochondria lead to loss of synapses and dendritic spines [75]. In contrast, increasing dendritic mitochondrial content or mitochondrial activity enhances the number and plasticity of synapses [75]. This way, the dendritic distribution of mitochondria can be both essential and limiting for the support of synapses [13, 75, 76]. Moreover, mitochondrial gene upregulation has been observed following synaptic and neuronal activity [75].

Mitochondrial dysfunction leads to alterations in ATP production and cytoplasmatic calcium concentrations, reactive oxygen species, and nitric oxide production [77]. Mitochondria dysfunction has been implicated in the defective processes of plasticity occurring in schizophrenia [77].

Therefore, the spatiotemporal dynamic patterns of mitochondrial distribution can work as a "mitochondrial memory code" that dictates the potentiation of specific synapses and the plasticity of the neuronal network [78].

4.3. Structural Plasticity in the Visual Cortex. Animals under environmental enrichment (cages containing toys that are frequently changed) develop an increase in brain weight and cortical thickness, including the occipital cortex. Similarly, grey matter macrostructure changes have been reported in humans after juggling training, aerobic exercise, and intense language studies [16, 79–82]. Volume and thickness changes are specific to those brain regions that are functionally relevant for the trained task [83].

Neurochemical changes consisting of an increase in N-acetylaspartate (available almost only in neurons) were detected with magnetic resonance spectroscopy in adult men after a period of navigation training [79].

However, the existence of structural plasticity in the human primary visual cortex is controversial. It has been argued that both the location and apparent time course of structural changes vary substantially between studies, despite

the similarity of the training paradigms [84]. Moreover, the reliability of voxel-based morphometry as a method for investigating structural brain changes has been questioned, as well as the biological substrate of the reported structural changes [84, 85]. In addition, studies involving cortical plasticity in the context of retinal lesions in humans have important limitations, as it is not possible to exclude spared retinal regions or changing borders in the absence of histological examination [85, 86]. It is also possible that V1 responses in the presence of central retinal lesions are due to activation via extrastriate cortex or subcortical structures [85, 87].

Despite the absence of large-scale structural remodeling later in life, the reorganization of cortical connections in terms of growth and loss of dendritic spines may be the structural substrate for experience-dependent plasticity [62].

In conclusion, the biological background of visual plasticity involves several mechanisms which are still incompletely characterized and controversial (Figure 1). Understanding these mechanisms will be important for a better recognition of the occurrence of plasticity and for disease treatment. As stated by Wandell and Smirnakis [85], it is not worth having a debate as to whether the brain is plastic or not: it is both. It is more important to study the conditions under which each system is stable or plastic.

5. Question 4: What Is the Relevance of Visual Plasticity for Ophthalmology?

5.1. Plasticity in the Context of Retinal Disorders. Retinitis pigmentosa (RP) consists in an inherited progressive degeneration of photoreceptors, starting at the midperipheral (rod cells) and advancing towards the central retina (cone cells), with a subsequent deterioration of the retinal pigment epithelium. The absence or the segregation of mutated proteins provokes alterations in the regulated environment of rods. These cells undergo apoptosis, leading to a posterior degeneration of cones (it is believed that bipolar cells remain intact). The age of onset varies from infancy to adulthood, although the typical manifestations start at adolescence, making RP an appropriate way to study adult visual cortical plasticity [88, 89]. A recent fMRI study found visual cortical activation on the lesion projection zone (LPZ—region of visual cortex that is deprived of retinal input) [90] in striate areas of RP patients, during the performance of a visual task, in contrast with passive viewing stimulation. Authors suggested the unmasking of preexisting extrastriate feedback signals, which are blocked by lateral geniculate nucleus gating signals in the case of a healthy retina. However, the authors excluded the existence of large-scale reorganization, such as cortical rewiring or upregulation of existing synaptic connections [91, 92]. Another fMRI study showed crossmodal activity in the primary visual cortex of late-blind RP subjects during tactile tasks, while blindfolded. The authors also described a relationship between the level and the extension of cortical activation and the degree of vision loss in RP, suggesting adult cortical reorganization [93]. Parisi and coworkers used cortical visually evoked potentials to evaluate the relationship between retinal degeneration and visual cortical activation in RP individuals, encountering evidence of neural reorganization [94]. Wittich and colleagues described behavioral evidence of visual cortex plasticity, showing that RP patients have a similar ability to make spatial judgments as healthy subjects, despite the declining of their ocular function [92]. On the other hand, other studies did not report visual cortex reorganization in individuals with RP [95, 96].

Macular degeneration (MD), in contrast with RP, mainly affects the macula of the retina causing a progressive central vision loss. This disorder is associated with genetic mutations and environmental influences (aging, smoking, and diet). Wet MD is characterized by choroidal neovascularization that leads to an abnormal segregation of fluid or blood. Dry MD is more common and is caused by the accumulation of subretinal deposits and/or by hypo- or hyperpigmentation of retinal pigment epithelium. MD can affect elderly individuals—age-related macular degeneration (AMD)—or younger patients—juvenile macular degeneration (JMD). Thus, it is also a suitable model to analyze adult visual cortical plasticity [97]. Patients usually adopt a less stable peripheral retinal region for fixation without training or instruction—preferred retinal locus (PRL)—because the foveal region is absent due to a central scotoma. Some studies claim that this process results from primary visual cortex reorganization because deafferented neurons in LPZ become responsive to inputs near the retinal lesion, and the PRL is usually located in this area [98, 99]. An fMRI study identified activation of the LPZ with stimuli presented at the PRL or at another isoeccentric retinal location, indicating that reorganization is not driven by mechanisms related to the long-term use of PRL by patients, but it is instead a passive or spontaneous process [85, 98, 100]. Despite these results, the stimulation at PRL seems to be represented more extensively in visual cortex [101]. Another fMRI study presented different results where foveal cortex activation only exists for stimulation at PRL, correlating large-scale cortical reorganization and behavioral adaptations in MD. Authors proposed the enlargement of receptive fields, the strengthening of connections, extrastriate feedback, and/or changes in the network between visual areas and higher-order attention control areas as explanations for this reorganization [85, 99]. However, other authors did not report activation in the LPZ associated with the stimulation of the PRL [101, 102].

Another fMRI study with JMD and AMD patients indicated that visual stimulus falling on the peripheral retina activated the LPZ [85, 102]. Authors suggested the disinhibition/unmasking of intrinsic horizontal connections which spread activation from areas receiving retinal input to the LPZ, but this would require horizontal connections larger than normal V1 primate connections and polysynaptic chains of horizontal connections [102, 103]. They also proposed the growth of new horizontal connections, reorganization at precortical levels (but the previous literature reported absent or minimal reorganization at the lateral geniculate nucleus (LGN) and the retina), and top-down feedback from higher order visual areas associated with mental imagery and attention [85, 102–104]. In a later study, these authors concluded that this reorganization is only present for a completely loss of foveal vision, despite some possible local

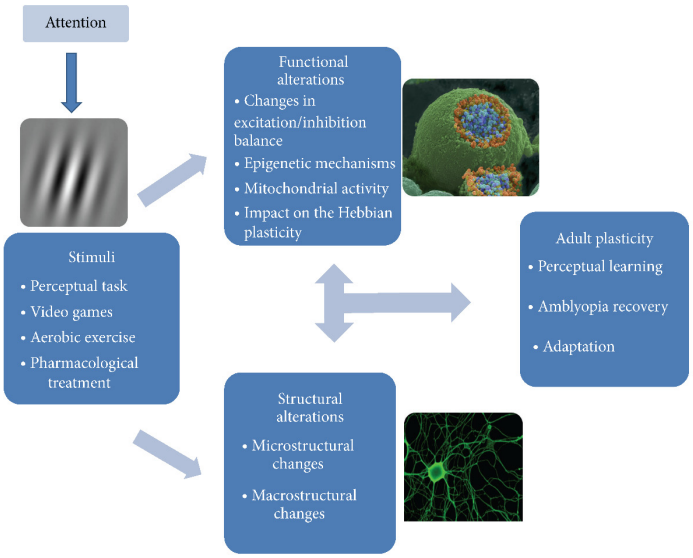

Figure 1: Plasticity in the adult visual cortex. In the presence of specific stimuli, such as performing a perceptual task, playing action video games, or pharmacological treatment, several functional alterations take place (image no. 214 from the Cell Image Library, neuron-neuron synaptic transmission). These include a decrease in inhibition/excitation ratio, epigenetic remodeling of chromatin structure, mitochondrial redistribution, activation of transcription factors, and protein synthesis. Structural plasticity includes modifications in neuronal morphology (axons, dendrites, and dendritic spines), suppression and creation of synapses, and genesis of new neurons and neuritis (image adapted from http://www.biomedcentral.com/1471-2202/6/24). The interplay of these mechanisms leads to adult neuronal plasticity, as revealed by the increased perception of a trained stimulus, improvement of visual function in amblyopia, and long-term adaptation to changes in the subject (such as cataract surgery) or in the environment. Plasticity is under the top-down influence of attention, as attention acts upon sensory signals at many levels to construct a selective representation of visual space.

reorganization on the border of the LPZ [87, 103]. The level of cortical reorganization was not dependent on the age of onset or the type of MD [103]. Liu and colleagues demonstrated an incomplete functional reorganization where the extent of the LPZ was smaller in active than in passive viewing tasks. This effect was more prominent in JMD patients, suggesting a possible role of the age of onset and the disease etiology. Authors explained the results with the strengthening of feedback signals from higher cortical areas, associated with attention, during the task performance [101]. Masuda and colleagues found activation in the LPZ in JMD patients during an fMRI task related to the visual stimulus, but not during the stimulus passive visualization or a task unrelated to the stimulus [87]. They justified their results with the unmasking of task-dependent extrastriate feedback signals in the absence of input from the lateral geniculate nucleus, related to attention, visual imagery, and task-related low-level visual processing. Although similar results have been considered evidence of reorganization [101], these authors did not name it cortical reorganization, arguing that there was no change in neuronal architecture (synaptic gain or axonal connections) [85, 86].

Despite the evidence of functional reorganization in the adult visual cortex of JMD and/or AMD patients, some fMRI studies have questioned its existence [85, 105–107]. fMRI studies with simulated (artificial) central scotomata in healthy subjects presented enlarged and displaced receptive fields of cortical neurons, suggesting receptive field position, size scatter, and feedback signals from extrastriate cortex, thus questioning visual cortical reorganization [106, 108].

Kaas and colleagues' single-cell records in adult cats with induced central scotomata in one eye and enucleation of the other eye showed that neurons at the border of the LPZ responded to input from the area surrounding the retinal lesion. Receptive field sizes and response characteristics in LPZ were similar to normal cells after 2–6 months of visual deprivation, but receptive fields were displaced in LPZ. The authors proposed that this was due to "changes in the effectiveness of synapses within the arbors of thalamocortical axons of previously existing inputs" [85, 109–111]. Other studies with adult cats and adult monkeys with bilateral central retinal lesions demonstrated cortical retinotopic reorganization for stimulation outside the retinal lesion, due to the rapid expansion and shift of receptive fields of neurons near the

border of the LPZ, some minutes after inducing scotomata, and due to long-range lateral cortical connections in the LPZ, after 2–12 months. However, the reorganization of LPZ was not complete, neuronal responses were weaker than normal, and the quality of orientation tuning of receptive fields was reduced [85, 104, 110, 111]. The short-term reorganization may be caused by the reweighting or the unmasking of existing neural connections. However, evidence for axonal and dendritic sprouting has also been identified in studies with adult cats as underlying mechanisms for long-term visual cortex reorganization [85, 87, 98, 99, 112].

However, the existence of visual plasticity following retinal lesions in animal models remains controversial. Horton et al. found that cytochrome oxidase levels in V1 remained severely depressed even months after monocular retinal lesions in adult macaques [113]. Similarly, Murakami et al. found no evidence for topographic reorganization after monocular retinal lesions, using electrophysiological recordings. Smirnakis et al. used a 4.7-T fMRI in adult macaques to evaluate the existence of long-term cortical reorganization after retinal lesions [112]. There was no significant change in the position and size of the LPZ, which was also confirmed by electrophysiological measurements. The reason for these conflicting results may be due to retinal recovery after swelling caused by photocoagulation lasers used to induce scotomata, because researchers compare cortical responses after inducing the lesion to responses several months later. In addition, it is possible that reorganization might be restricted to some specific neurons inside the LPZ [112].

In conclusion, the degree of adult visual cortical plasticity due to retinal diseases remains questionable. However, the current view is that the visual cortex is plastic into the adulthood, although this plasticity is limited after the critical period [85, 114, 115].

Several hypotheses have been established to explain visual cortical reorganization: (1) development of synapses to create new lateral connections within V1, (2) large increase of synaptic signals that carry feedback and lateral connections, (3) unmasking of existing feedback signals from higher order cortical areas into V1 by deletion of feedforward signals, (4) increase of sizes and shift of receptive fields into the LPZ, and (5) modifications at precortical stages of visual system, although previous analyses suggested an absent or minimal reorganization at retinal and lateral geniculate nucleus levels [85, 87, 91, 101–104, 110]. It is known that feedback signals into primary visual cortex arise from higher order visual areas, frontal and parietal cortices, and are involved in attention, visual imagery, and task-related visual processing [85, 87, 91, 103]. Structural alterations of the adult visual cortex (establishment of new connections through dendritic growth, sprouting, and arborization) seem to be associated with a long duration of visual diseases, following rapid changes associated with modifications in the strength or the unmasking of preexisting connections. This can explain the "difference of reorganization between early- and late-blind individuals" [114].

The major limitations of studies concerning this issue are the reduced number of subjects, the heterogeneity among patients (nature of scotomata, disease duration, and progression), and the variations in methodologies (measurement of attentional state of subjects, monocular versus binocular stimulation, and delineation of the LPZ). In addition, there are difficulties in measuring the activity of the same neuronal cells before and after lesion and in establishing plasticity mechanisms with neuroimaging (scale of reorganization of several centimeters) versus electrophysiological techniques (scale of reorganization of few millimeters) [85, 87, 91, 92, 103, 111].

Future investigations are important to quantify the level of adult brain plasticity in visual processing. There is a lack of studies concerning the effects of peripheral vision loss on visual cortex (the majority of the literature presented above addressed central vision disorders) and the relationship between structural and functional visual cortical reorganization.

5.2. Plasticity in the Context of Refractive Surgery. Anisometropia, a difference between the two eyes refractive errors generally exceeding 3 diopters, is an important cause of amblyopia. However, contrary to the expected persistency of visual deficiencies, refractive surgery (surgery that corrects refractive errors such as myopia, astigmatism, and hyperopia) is able to improve corrected visual acuity in amblyopic patients [116–118]. A study comparing fMRI activation patterns between preoperative and 12-month postoperative cortical maps found a decrease in the number of active voxels in the anisometropic fovea [119]. The proposed rationale for this finding was that before surgery a large network of neurons was activated for each visual stimulus. After surgery, however, only a subgroup of neurons is activated because stimuli processing has become more efficient [119]. This study thus provides evidence for plastic changes taking place in the primary visual cortex of adult anisometropic patients after refractive surgery and highlights the importance of visual plasticity even in the context of conditions requiring strictly ophthalmic procedures, such as refractive surgery.

5.3. Neuroadaptation to Presbyopia Correcting Intraocular Lenses. Presbyopia is the natural decline in near vision that occurs in human healthy aging. Surgical interventions to treat presbyopia and cataract are widely used, such as multifocal intraocular lenses, but they rely on the simultaneous presentation of distance and near images to the retina [120]. These lenses are associated with unwanted side effects, such as glare, halos, and loss of contrast sensitivity, that tend to improve over time in some patients, but not in others [121, 122]. These symptoms are usually more severe under low light (mesopic) conditions [123]. It is thought that the brain adapts to those unwanted stimuli, but it is unknown if it is an adaptive process or a form of perceptual learning. We hypothesize that multifocal intraocular lens may target different forms of plasticity, comprising (1) adaptation, triggered to decrease sensitivity to "background noise" images and glare, (2) perceptual learning, for better discrimination of low contrast targets, and (3) attention, to selectively see the image of interest despite the presence of two images (distance

and near) in focus. Despite the fact that it is generally accepted that the brain plays a major role in visual performance with these more complex intraocular lenses, which is referred as *neuroadaptation*, there are no studies available evaluating cortical activity in the presence of multifocal lenses [124–127]. Strategies to increase plasticity mechanisms in the early postoperative period would likely improve the performance and comfort with these and other novel lenses.

5.4. Amblyopia Treatment and the Reinstatement of Plasticity in the Adult Visual System. Amblyopia can be considered the result of a lack of normal plasticity. Visual cortical dominance by the better eye leads to correspondent visual deprivation of the representations related to the eye with worse acuity. Knowledge of neuroplasticity and the factors that control the opening and closure of critical periods will lead to new therapeutic strategies which may allow for greater recovery of visual functions in both children and adults with amblyopia [5]. As previously described, the developmental maturation of intracortical inhibitory circuitries causes the end of plasticity in the visual system. In keeping with this notion, it is possible to restore plasticity in adult life by reducing levels of inhibition [5]. A direct demonstration that GABAergic signaling is a crucial brake limiting visual cortex plasticity was derived from the observation that a pharmacological decrease of inhibitory transmission effectively restores ocular dominance plasticity in adulthood [62]. Indeed, intracortical inhibitory circuitry has now emerged as a key factor in defining the limits of cortical plasticity [5]. It has thus been hypothesized that a critical factor in restoring plasticity and inducting recovery from amblyopia is to increase the ratio between excitation (glutamate receptors) and inhibition (GABA receptors) by reducing intracortical inhibition. In rodent models, plasticity can be elicited by reducing intracortical inhibition through pharmacologic treatment with administration of antidepressants [5, 67]. In humans, memantine, a glutamate receptor antagonist, abolishes a form of long-term potentiation plasticity. The GABAergic drugs diazepam, tiagabine, and baclofen also reduce this form of plasticity [57].

Amblyopia treatment has mainly involved performing perceptual learning tasks, such as contrast detection tasks with Gabor signals, as mentioned previously [8]. Improvement in visual acuity has been shown even when the training involves practicing a very different and functionally more basic task [8]. Similarly, Li et al. showed that after a brief period of video-game play a wide range of spatial vision functions improved substantially, reflecting normalization of visual acuity and positional acuity (low-level visual processing) and high-level processing (spatial attention, stereoacuity) [14].

5.5. Maladaptive Plasticity. In maladaptive plasticity there is a behavioral loss or the appearance of disease symptoms resulting from plasticity changes in the adult human brain [4].

Brain morphologic alterations in areas responsible for the transmission of pain were detected in patients suffering from different forms of pain, such as phantom pain, chronic back pain, neuropathic pain, irritable bowel syndrome, fibromyalgia, and headaches [128, 129].

Plasticity also underlies addiction-related processes, such as drug sensitization, drug seeking, and hypofrontality. Psychostimulant drugs such as amphetamine and cocaine are prototypic drugs inducing neuroplasticity changes [55].

Charles Bonnet syndrome can be thought as a form of maladaptive visual plasticity. This syndrome is characterized by complex, formed hallucinations occurring not only in patients without psychiatric disorders, usually after profound visual loss, but also in patients with visual field defects and normal central visual acuity [130–133]. Tan et al. proposed that after deafferentation caused by retinal or cortical lesions, the neurons become more responsive to neurotransmitter release by increasing the number and/or sensitivity of postsynaptic receptors [134]. Due to this increased sensitivity, normal levels of intracortical input trigger visual hallucinations. Because hallucinations tend to occur during visual recovery, the authors suggest that they are a correlate of visual system plasticity [134]. In this context, although they are usually a cause of concern, they may be a good prognostic sign, indicating the occurrence of neuroplasticity and visual field recovery [134].

Another downside of plasticity in the context of ophthalmology has been highlighted by Baseler et al. As the authors state, many of the most promising treatments for severe retinal disorders, such as prosthetics and stemcell therapy, rely on the assumption that the remaining cortical circuitry remains unchanged. This means that if it is possible to restore the input to the visual cortex, with novel retinal therapies, the neurons would be able to process this input effectively. Large scale plasticity could therefore jeopardize the effectiveness of these treatments.

6. General Conclusions

In conclusion, there are several forms of plasticity that remain largely functional in the adult visual system, as exemplified by perceptual learning and long-term adaptation. Both changes in the environment and in the observer are likely to involve different forms of plasticity that act together for perceptual optimization. Several biological systems are implicated in the interplay of functional and structural plasticity. Understanding how these mechanisms work could pave the way for new forms of diagnosis and treatment of ophthalmic disorders, comprising rehabilitation after severe retinal disorders, amblyopia treatment, and improvement of surgical results after cataract and refractive surgery.

Conflict of Interests

The authors have no financial or proprietary interests in any material or method mentioned.

References

[1] C. A. Nelson, "Neural plasticity and human development: the role of early experience in sculpting memory systems," *Developmental Science*, vol. 3, no. 2, pp. 115–136, 2000.

[2] D. Bavelier, D. M. Levi, R. W. Li, Y. Dan, and T. K. Hensch, "Removing brakes on adult brain plasticity: from molecular to behavioral interventions," *The Journal of Neuroscience*, vol. 30, no. 45, pp. 14964–14971, 2010.

[3] A. Miki, J. C. Haselgrove, and G. T. Liu, "Functional magnetic resonance imaging and its clinical utility in patients with visual disturbances," *Survey of Ophthalmology*, vol. 47, no. 6, pp. 562–579, 2002.

[4] A. May, "Experience-dependent structural plasticity in the adult human brain," *Trends in Cognitive Sciences*, vol. 15, no. 10, pp. 475–482, 2011.

[5] A. M. Wong, "New concepts concerning the neural mechanisms of amblyopia and their clinical implications," *Canadian Journal of Ophthalmology*, vol. 5, pp. 399–409, 2012.

[6] D. Maurer, T. L. Lewis, and C. J. Mondloch, "Missing sights: consequences for visual cognitive development," *Trends in Cognitive Sciences*, vol. 9, no. 3, pp. 144–151, 2005.

[7] M. Bedny, T. Konkle, K. Pelphrey, R. Saxe, and A. Pascual-Leone, "Sensitive period for a multimodal response in human visual motion area MT/MST," *Current Biology*, vol. 20, no. 21, pp. 1900–1906, 2010.

[8] U. Polat, T. Ma-Naim, M. Belkin, and D. Sagi, "Improving vision in adult amblyopia by perceptual learning," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 101, no. 17, pp. 6692–6697, 2004.

[9] R. W. Li, K. G. Young, P. Hoenig, and D. M. Levi, "Perceptual learning improves visual performance in juvenile amblyopia," *Investigative Ophthalmology and Visual Science*, vol. 46, no. 9, pp. 3161–3168, 2005.

[10] Y. Zhou, C. Huang, P. Xu et al., "Perceptual learning improves contrast sensitivity and visual acuity in adults with anisometropic amblyopia," *Vision Research*, vol. 46, no. 5, pp. 739–750, 2006.

[11] S. T. L. Chung, R. W. Li, and D. M. Levi, "Identification of contrast-defined letters benefits from perceptual learning in adults with amblyopia," *Vision Research*, vol. 46, no. 22, pp. 3853–3861, 2006.

[12] L.-Q. Xiao, J.-Y. Zhang, R. Wang, S. A. Klein, D. M. Levi, and C. Yu, "Complete transfer of perceptual learning across retinal locations enabled by double training," *Current Biology*, vol. 18, no. 24, pp. 1922–1926, 2008.

[13] O. C. d'Almeida, C. Mateus, A. Reis, M. M. Grazina, and M. Castelo-Branco, "Long term cortical plasticity in visual retinotopic areas in humans with silent retinal ganglion cell loss," *Neuroimage*, vol. 81, pp. 222–230, 2013.

[14] R. W. Li, C. Ngo, J. Nguyen, and D. M. Levi, "Video-game play induces plasticity in the visual system of adults with amblyopia," *PLoS Biology*, vol. 9, no. 8, Article ID e1001135, 2011.

[15] U. R. Karmarkar and Y. Dan, "Experience-dependent plasticity in adult visual cortex," *Neuron*, vol. 52, no. 4, pp. 577–585, 2006.

[16] J. Scholz, M. C. Klein, T. E. J. Behrens, and H. Johansen-Berg, "Training induces changes in white-matter architecture," *Nature Neuroscience*, vol. 12, no. 11, pp. 1370–1371, 2009.

[17] P. M. Greenwood, "Functional plasticity in cognitive aging: review and hypothesis," *Neuropsychology*, vol. 21, no. 6, pp. 657–673, 2007.

[18] S. Schwartz, "Functional MRI evidence for neural plasticity at early stages of visual processing in humans," in *Object Recognition, Attention, and Action*, N. Osaka, I. Rentschler, and I. Biederman, Eds., pp. 27–40, Springer, Tokyo, Japan, 2007.

[19] S. Schwartz, P. Maquet, and C. Frith, "Neural correlates of perceptual learning: a functional MRI study of visual texture discrimination," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 99, no. 26, pp. 17137–17142, 2002.

[20] C. S. Furmanski, D. Schluppeck, and S. A. Engel, "Learning strengthens the response of primary visual cortex to simple patterns," *Current Biology*, vol. 14, no. 7, pp. 573–578, 2004.

[21] C. D. Gilbert, M. Sigman, and R. E. Crist, "The neural basis of perceptual learning," *Neuron*, vol. 31, no. 5, pp. 681–697, 2001.

[22] N. K. Logothetis, J. Pauls, M. Augath, T. Trinath, and A. Oeltermann, "Neurophysiological investigation of the basis of the fMRI signal," *Nature*, vol. 412, no. 6843, pp. 150–157, 2001.

[23] J. Feng, I. Spence, and J. Pratt, "Playing an action video game reduces gender differences in spatial cognition," *Psychological Science*, vol. 18, no. 10, pp. 850–855, 2007.

[24] R. L. Goldstone, "Perceptual learning," *Annual Review of Psychology*, vol. 49, pp. 585–612, 1998.

[25] T. Moore and K. M. Armstrong, "Selective gating of visual signals by microstimulation of frontal cortex," *Nature*, vol. 421, no. 6921, pp. 370–373, 2003.

[26] W. Li, V. Piëch, and C. D. Gilbert, "Perceptual learning and top-down influences in primary visual cortex," *Nature Neuroscience*, vol. 7, no. 6, pp. 651–657, 2004.

[27] D. Sagi, "Perceptual learning in vision research," *Vision Research*, vol. 51, no. 13, pp. 1552–1566, 2011.

[28] H. Harris, M. Gliksberg, and D. Sagi, "Generalized perceptual learning in the absence of sensory adaptation," *Current Biology*, vol. 19, pp. 1813–1817, 2012.

[29] I. Mukai, D. Kim, M. Fukunaga, S. Japee, S. Marrett, and L. G. Ungerleider, "Activations in visual and attention-related areas predict and correlate with the degree of perceptual learning," *The Journal of Neuroscience*, vol. 27, no. 42, pp. 11401–11411, 2007.

[30] J. I. Gold and M. N. Shadlen, "The neural basis of decision making," *Annual Review of Neuroscience*, vol. 30, pp. 535–574, 2007.

[31] L. P. Shiu and H. Pashler, "Improvement in line orientation discrimination is retinally local but dependent on cognitive set," *Perception and Psychophysics*, vol. 52, no. 5, pp. 582–588, 1992.

[32] M. Ahissar and S. Hochstein, "Attentional control of early perceptual learning," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 90, no. 12, pp. 5718–5722, 1993.

[33] D. Schneider, C. Beste, and E. Wascher, "On the time course of bottom-up and top-down processes in selective visual attention: an EEG study," *Psychophysiology*, vol. 11, pp. 1492–1503, 2012.

[34] D. C. Somers, A. M. Dale, A. E. Seiffert, and R. B. H. Tootell, "Functional MRI reveals spatially specific attentional modulation in human primary visual cortex," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 96, no. 4, pp. 1663–1668, 1999.

[35] N. Lavie, "Distracted and confused?: selective attention under load," *Trends in Cognitive Sciences*, vol. 9, no. 2, pp. 75–82, 2005.

[36] S. Schwartz, P. Vuilleumier, C. Hutton, A. Maravita, R. J. Dolan, and J. Driver, "Attentional load and sensory competition in human vision: modulation of fMRI responses by load at fixation during task-irrelevant stimulation in the peripheral visual field," *Cerebral Cortex*, vol. 15, no. 6, pp. 770–786, 2005.

[37] M. Carrasco, "Covert attention increases contrast sensitivity: psychophysical, neurophysiological and neuroimaging studies," *Progress in Brain Research*, vol. 154, pp. 33–70, 2006.

[38] S. Kastner and L. G. Ungerleider, "The neural basis of biased competition in human visual cortex," *Neuropsychologia*, vol. 39, no. 12, pp. 1263–1276, 2001.

[39] R. Berman and C. Colby, "Attention and active vision," *Vision Research*, vol. 49, no. 10, pp. 1233–1248, 2009.

[40] M. Carrasco, M. Eckstein, R. Krauzlis, and P. Verghese, "Vision research special issue on 'visual attention'," *Vision Research*, vol. 74, article 1, 2012.

[41] M. Carrasco, "Cross-modal attention enhances perceived contrast," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 52, pp. 22039–22040, 2009.

[42] M. R. Kamke, M. G. Hall, H. F. Lye et al., "Visual attentional load influences plasticity in the human motor cortex," *The Journal of Neuroscience*, vol. 20, pp. 7001–7008, 2012.

[43] M. A. Webster, "Adaptation and visual coding," *Journal of Vision*, vol. 11, no. 5, pp. 1–23, 2011.

[44] P. Thompson and D. Burr, "Visual aftereffects," *Current Biology*, vol. 19, no. 1, pp. R11–R14, 2009.

[45] O. Yehezkel, D. Sagi, A. Sterkin, M. Belkin, and U. Polat, "Learning to adapt: dynamics of readaptation to geometrical distortions," *Vision Research*, vol. 50, no. 16, pp. 1550–1558, 2010.

[46] S. C. Belmore and S. K. Shevell, "Very-long-term chromatic adaptation: test of gain theory and a new method," *Visual Neuroscience*, vol. 25, no. 3, pp. 411–414, 2008.

[47] M. Kwon, G. E. Legge, F. Fang, A. M. Y. Cheong, and S. He, "Adaptive changes in visual cortex following prolonged contrast reduction," *Journal of Vision*, vol. 9, no. 2, pp. 1–16, 2009.

[48] M. Mon-Williams, J. R. Tresilian, N. C. Strang, P. Kochhar, and J. P. Wann, "Improving vision: neural compensation for optical defocus," *Proceedings of the Royal Society B*, vol. 265, no. 1390, pp. 71–77, 1998.

[49] D. M. Levi and R. W. Li, "Perceptual learning as a potential treatment for amblyopia: a mini-review," *Vision Research*, vol. 49, no. 21, pp. 2535–2549, 2009.

[50] Z.-L. Lu, C. Yu, T. Watanabe, D. Sagi, and D. Levi, "Perceptual learning: functions, mechanisms, and applications," *Vision Research*, vol. 49, no. 21, pp. 2531–2534, 2009.

[51] A. F. Teich and N. Qian, "Learning and adaptation in a recurrent model of V1 orientation selectivity," *Journal of Neurophysiology*, vol. 89, no. 4, pp. 2086–2100, 2003.

[52] L. Sawides, S. Marcos, S. Ravikumar, L. Thibos, A. Bradley, and M. Webster, "Adaptation to astigmatic blur," *Journal of Vision*, vol. 10, no. 12, p. 22, 2010.

[53] A. Werner, A. Bayer, G. Schwarz, E. Zrenner, and W. Paulus, "Effects of ageing on postreceptoral short-wavelength gain control: transient tritanopia increases with age," *Vision Research*, vol. 50, no. 17, pp. 1641–1648, 2010.

[54] J. Rivest, J. S. Kim, J. Intriligator, and J. A. Sharpe, "Effect of aging on visual shape distortion," *Gerontology*, vol. 50, no. 3, pp. 142–151, 2004.

[55] E. Fernandez-Espejo and N. Rodriguez-Espinosa, "Psychostimulant drugs and neuroplasticity," *Pharmaceuticals*, vol. 4, no. 7, pp. 976–991, 2011.

[56] T. V. P. Bliss and T. Lomo, "Long lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path," *Journal of Physiology*, vol. 232, no. 2, pp. 331–356, 1973.

[57] M. A. Nitsche, F. Muller-Dahlhaus, W. Paulus, and U. Ziemann, "The pharmacology of neuroplasticity induced by non-invasive brain stimulation: building models for the clinical use of CNS active drugs," *Journal of Physiology*, vol. 19, pp. 4641–4662, 2012.

[58] T. K. Hensch, "Critical period plasticity in local cortical circuits," *Nature Reviews Neuroscience*, vol. 6, no. 11, pp. 877–888, 2005.

[59] M. Fagiolini and T. K. Hensch, "Inhibitory threshold for critical-period activation in primary visual cortex," *Nature*, vol. 404, no. 6774, pp. 183–186, 2000.

[60] B. Boroojerdi, F. Battaglia, W. Muellbacher, and L. G. Cohen, "Mechanisms underlying rapid experience-dependent plasticity in the human visual cortex," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 98, no. 25, pp. 14698–14701, 2001.

[61] A. W. McGee, Y. Yang, Q. S. Fischer, N. W. Daw, and S. M. Strittmatter, "Experience-driven plasticity of visual cortex limited by myelin and Nogo receptor," *Science*, vol. 5744, pp. 2222–2226, 2005.

[62] J. F. Maya-Vetencourt and N. Origlia, "Visual cortex plasticity: a complex interplay of genetic and environmental influences," *Neural Plasticity*, vol. 2012, Article ID 631965, 14 pages, 2012.

[63] V. H. Minces, A. S. Alexander, M. Datlow, S. I. Alfonso, and A. A. Chiba, "The role of visual cortex acetylcholine in learning to discriminate temporally modulated visual stimuli," *Frontiers in Behavioral Neuroscience*, vol. 7, article 16, 2013.

[64] A. A. Chubykin, E. B. Roach, M. F. Bear, and M. G. Shuler, "A cholinergic mechanism for reward timing within primary visual cortex," *Neuron*, vol. 4, pp. 723–735, 2013.

[65] C. Crosio, E. Heitz, C. D. Allis, E. Borrelli, and P. Sassone-Corsi, "Chromatin remodeling and neuronal response: multiple signaling pathways induce specific histone H3 modifications and early gene expression in hippocampal neurons," *Journal of Cell Science*, vol. 116, no. 24, pp. 4905–4914, 2003.

[66] T.-Y. Zhang and M. J. Meaney, "Epigenetics and the environmental regulation of the genome and its function," *Annual Review of Psychology*, vol. 61, pp. 439–466, 2010.

[67] J. F. M. Vetencourt, E. Tiraboschi, M. Spolidoro, E. Castrén, and L. Maffei, "Serotonin triggers a transient epigenetic mechanism that reinstates adult visual cortex plasticity in rats," *European Journal of Neuroscience*, vol. 33, no. 1, pp. 49–57, 2011.

[68] J. M. Levenson and J. D. Sweatt, "Epigenetic mechanisms: a common theme in vertebrate and invertebrate memory formation," *Cellular and Molecular Life Sciences*, vol. 63, no. 9, pp. 1009–1016, 2006.

[69] T. A. Pham, S. J. Graham, S. Suzuki et al., "A semi-persistent adult ocular dominance plasticity in visual cortex is stabilized by activated CREB," *Learning and Memory*, vol. 11, no. 6, pp. 738–747, 2004.

[70] R. J. Kelleher III, A. Govindarajan, and S. Tonegawa, "Translational regulatory mechanisms in persistent forms of synaptic plasticity," *Neuron*, vol. 44, no. 1, pp. 59–73, 2004.

[71] J. Seibt, M. C. Dumoulin, S. J. Aton et al., "Protein synthesis during sleep consolidates cortical plasticity in vivo," *Current Biology*, vol. 22, no. 8, pp. 676–682, 2012.

[72] I. Bókkon and R. L. P. Vimal, "Implications on visual apperception: energy, duration, structure and synchronization," *BioSystems*, vol. 101, no. 1, pp. 1–9, 2010.

[73] M. P. Mattson, "Mitochondrial regulation of neuronal plasticity," *Neurochemical Research*, vol. 32, no. 4-5, pp. 707–715, 2007.

[74] J. E. Black, A. M. Zelazny, and W. T. Greenough, "Capillary and mitochondrial support of neural plasticity in adult rat visual cortex," *Experimental Neurology*, vol. 111, no. 2, pp. 204–209, 1991.

[75] Z. Li, K.-I. Okamoto, Y. Hayashi, and M. Sheng, "The importance of dendritic mitochondria in the morphogenesis and plasticity of spines and synapses," *Cell*, vol. 119, no. 6, pp. 873–887, 2004.

[76] R. S. Stowers, L. J. Megeath, J. Górska-Andrzejak, I. A. Meinertzhagen, and T. L. Schwarz, "Axonal transport of mitochondria to synapses depends on Milton, a novel Drosophila protein," *Neuron*, vol. 36, no. 6, pp. 1063–1077, 2002.

[77] D. Ben-Shachar and D. Laifenfeld, "Mitochondria, synaptic plasticity, and schizophrenia," *International Review of Neurobiology*, vol. 59, pp. 273–296, 2004.

[78] J. J. Tong, "Mitochondrial delivery is essential for synaptic potentiation," *Biological Bulletin*, vol. 212, no. 2, pp. 169–175, 2007.

[79] M. Lovden, E. Wenger, J. Martensson, U. Lindenberger, and L. Backman, "Structural brain plasticity in adult learning and development," *Neuroscience & Biobehavioral Reviews*, 2013.

[80] B. Draganski, C. Gaser, V. Busch, G. Schuierer, U. Bogdahn, and A. May, "Neuroplasticity: changes in grey matter induced by training," *Nature*, vol. 6972, pp. 311–312, 2004.

[81] J. Boyke, J. Driemeyer, C. Gaser, C. Büchel, and A. May, "Training-induced brain structure changes in the elderly," *The Journal of Neuroscience*, vol. 28, no. 28, pp. 7031–7035, 2008.

[82] J. Driemeyer, J. Boyke, C. Gaser, C. Büchel, and A. May, "Changes in gray matter induced by learning—revisited," *PLoS ONE*, vol. 3, no. 7, Article ID e2669, 2008.

[83] R. Ilg, A. M. Wohlschläger, C. Gaser et al., "Gray matter increase induced by practice correlates with task-specific activation: a combined functional and morphometric magnetic resonance imaging study," *The Journal of Neuroscience*, vol. 28, no. 16, pp. 4210–4215, 2008.

[84] C. Thomas and C. I. Baker, "Remodeling human cortex through training: comment on May," *Trends in Cognitive Sciences*, vol. 16, no. 2, pp. 96–97, 2012.

[85] B. A. Wandell and S. M. Smirnakis, "Plasticity and stability of visual field maps in adult primary visual cortex," *Nature Reviews Neuroscience*, vol. 10, no. 12, pp. 873–884, 2009.

[86] Y. M. Paulus, A. Jain, R. F. Gariano et al., "Healing of retinal photocoagulation lesions," *Investigative Ophthalmology and Visual Science*, vol. 49, no. 12, pp. 5540–5545, 2008.

[87] Y. Masuda, S. O. Dumoulin, S. Nakadomari, and B. A. Wandell, "V1 projection zone signals in human macular degeneration depend on task, not stimulus," *Cerebral Cortex*, vol. 18, no. 11, pp. 2483–2493, 2008.

[88] M. A. Musarella and I. M. Macdonald, "Current concepts in the treatment of retinitis pigmentosa," *Journal of Ophthalmology*, vol. 2011, Article ID 753547, 8 pages, 2011.

[89] C. Hamel, "Retinitis pigmentosa," *Orphanet Journal of Rare Diseases*, vol. 1, no. 1, article 40, 2006.

[90] L. M. Schmid, M. G. P. Rosa, M. B. Calford, and J. S. Ambler, "Visuotopic reorganization in the primary visual cortex of adult cats following monocular and binocular retinal lesions," *Cerebral Cortex*, vol. 6, no. 3, pp. 388–405, 1996.

[91] Y. Masuda, H. Horiguchi, S. O. Dumoulin et al., "Task-dependent V1 responses in human retinitis pigmentosa," *Investigative Ophthalmology and Visual Science*, vol. 51, no. 10, pp. 5356–5364, 2010.

[92] W. Wittich, J. Faubert, D. H. Watanabe, M. A. Kapusta, and O. Overbury, "Spatial judgments in patients with retinitis pigmentosa," *Vision Research*, vol. 51, no. 1, pp. 165–173, 2011.

[93] S. I. Cunningham, J. D. Weiland, P. Bao, and B. S. Tjan, "Visual cortex activation induced by tactile stimulation in late-blind individuals with retinitis pigmentosa," in *Proceedings of the 33rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBS '11)*, pp. 2841–2844, September 2011.

[94] V. Parisi, L. Ziccardi, G. Stifano, L. Montrone, G. Gallinaro, and B. Falsini, "Impact of regional retinal responses on cortical visually evoked responses: multifocal ERGs and VEPs in the retinitis pigmentosa model," *Clinical Neurophysiology*, vol. 121, no. 3, pp. 380–385, 2010.

[95] J. Jiang, W. Zhu, F. Shi et al., "Thick visual cortex in the early blind," *The Journal of Neuroscience*, vol. 29, no. 7, pp. 2205–2211, 2009.

[96] J. Xie, G.-J. Wang, L. Yow et al., "Preservation of retinotopic map in retinal degeneration," *Experimental Eye Research*, vol. 98, no. 1, pp. 88–96, 2012.

[97] S. Haddad, C. A. Chen, S. L. Santangelo, and J. M. Seddon, "The genetics of age-related macular degeneration: a review of progress to date," *Survey of Ophthalmology*, vol. 51, no. 4, pp. 316–363, 2006.

[98] S.-H. Cheung and G. E. Legge, "Functional and cortical adaptations to central vision loss," *Visual Neuroscience*, vol. 22, no. 2, pp. 187–201, 2005.

[99] E. H. Schumacher, J. A. Jacko, S. A. Primo et al., "Reorganization of visual processing is related to eccentric viewing in patients with macular degeneration," *Restorative Neurology and Neuroscience*, vol. 26, no. 4-5, pp. 391–402, 2008.

[100] D. D. Dilks, C. I. Baker, E. Peli, and N. Kanwisher, "Reorganization of visual processing in macular degeneration is not specific to the 'preferred retinal locus'," *The Journal of Neuroscience*, vol. 29, no. 9, pp. 2768–2773, 2009.

[101] T. Liu, S.-H. Cheung, R. A. Schuchard et al., "Incomplete cortical reorganization in macular degeneration," *Investigative Ophthalmology and Visual Science*, vol. 51, no. 12, pp. 6826–6834, 2010.

[102] C. I. Baker, E. Peli, N. Knouf, and N. G. Kanwisher, "Reorganization of visual processing in macular degeneration," *The Journal of Neuroscience*, vol. 25, no. 3, pp. 614–618, 2005.

[103] C. I. Baker, D. D. Dilks, E. Peli, and N. Kanwisher, "Reorganization of visual processing in macular degeneration: replication and clues about the role of foveal loss," *Vision Research*, vol. 48, no. 18, pp. 1910–1919, 2008.

[104] C. Darian-Smith and C. D. Gilbert, "Topographic reorganization in the striate cortex of the adult cat and monkey is cortically mediated," *The Journal of Neuroscience*, vol. 15, no. 3 I, pp. 1631–1647, 1995.

[105] J. S. Sunness, T. Liu, and S. Yantis, "Retinotopic mapping of the visual cortex using functional magnetic resonance imaging in a patient with central scotomas from atrophic macular degeneration," *Ophthalmology*, vol. 111, no. 8, pp. 1595–1598, 2004.

[106] H. A. Baseler, A. Gouws, K. V. Haak et al., "Large-scale remapping of visual cortex is absent in adult humans with macular degeneration," *Nature Neuroscience*, vol. 14, no. 5, pp. 649–655, 2011.

[107] C. C. Boucard, A. T. Hernowo, R. P. Maguire et al., "Changes in cortical grey matter density associated with long-standing

retinal visual field defects," *Brain*, vol. 132, no. 7, pp. 1898–1906, 2009.

[108] K. V. Haak, F. W. Cornelissen, and A. B. Morland, "Population receptive field dynamics in human visual cortex," *PLoS One*, vol. 7, no. 5, Article ID e37686, 2012.

[109] J. H. Kaas, L. A. Krubitzer, Y. M. Chino, A. L. Langston, E. H. Polley, and N. Blair, "Reorganization of retinotopic cortical maps in adult mammals after lesions of the retina," *Science*, vol. 248, no. 4952, pp. 229–231, 1990.

[110] S. J. Heinen and A. A. Skavenski, "Recovery of visual responses in foveal V1 neurons following bilateral foveal lesions in adult monkey," *Experimental Brain Research*, vol. 83, no. 3, pp. 670–674, 1991.

[111] D. V. Giannikopoulos and U. T. Eysel, "Dynamics and specificity of cortical map reorganization after retinal lesions," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 103, no. 28, pp. 10805–10810, 2006.

[112] S. M. Smirnakis, A. A. Brewer, M. C. Schmid et al., "Lack of long-term cortical reorganization after macaque retinal lesions," *Nature*, vol. 435, no. 7040, pp. 300–307, 2005.

[113] J. C. Horton and D. R. Hocking, "Monocular core zones and binocular border strips in primate striate cortex revealed by the contrasting effects of enucleation, eyelid suture, and retinal laser lesions on cytochrome oxidase activity," *The Journal of Neuroscience*, vol. 18, no. 14, pp. 5433–5455, 1998.

[114] A. Pascual-Leone, A. Amedi, F. Fregni, and L. B. Merabet, "The plastic human brain cortex," *Annual Review of Neuroscience*, vol. 28, pp. 377–401, 2005.

[115] L. B. Merabet and A. Pascual-Leone, "Neural reorganization following sensory loss: the opportunity of change," *Nature Reviews Neuroscience*, vol. 11, no. 1, pp. 44–52, 2010.

[116] C. Arruabarrena, M. A. Teus, J. L. Hernández-Verdejo, and R. Caones, "Visual acuity after laser in situ keratomileusis to correct high astigmatism in adults with meridional amblyopia," *American Journal of Ophthalmology*, vol. 152, no. 6, pp. 964.e1–968.e1, 2011.

[117] M. Paciuc, "Amblyopic adult eyes after LASIK," *Journal of Cataract and Refractive Surgery*, vol. 31, no. 12, pp. 2244–2245, 2005.

[118] F. Oruçoğlu, J. Frucht-Pery, D. Landau, E. Strasman, and S. Abraham, "LASIK correction of vision in adults with unilateral amblyopia," *Journal of Refractive Surgery*, vol. 27, no. 1, pp. 18–22, 2011.

[119] E. Vuori, S. Vanni, L. Henriksson, T. M. T. Tervo, and J. M. Holopainen, "Refractive surgery in anisometropic adult patients induce plastic changes in primary visual cortex," *Acta Ophthalmologica*, vol. 7, pp. 669–676, 2012.

[120] B. Agresta, M. C. Knorz, T. Kohnen, C. Donatti, and D. Jackson, "Distance and near visual acuity improvement after implantation of multifocal intraocular lenses in cataract patients with presbyopia: a systematic review," *Journal of Refractive Surgery*, vol. 6, pp. 426–435, 2012.

[121] N. E. de Vries, C. A. B. Webers, W. R. H. Touwslager et al., "Dissatisfaction after implantation of multifocal intraocular lenses," *Journal of Cataract and Refractive Surgery*, vol. 37, no. 5, pp. 859–865, 2011.

[122] K. Shimizu and M. Ito, "Dissatisfaction after bilateral multifocal intraocular lens implantation: an electrophysiology study," *Journal of Refractive Surgery*, vol. 27, no. 4, pp. 309–312, 2011.

[123] M. A. Woodward, J. B. Randleman, and R. D. Stulting, "Dissatisfaction after multifocal intraocular lens implantation," *Journal of Cataract and Refractive Surgery*, vol. 35, no. 6, pp. 992–997, 2009.

[124] S. M. Pepin, "Neuroadaptation of presbyopia-correcting intraocular lenses," *Current Opinion in Ophthalmology*, vol. 19, no. 1, pp. 10–12, 2008.

[125] R. Fernandez-Buenaga, J. L. Alio, F. J. Munoz-Negrete, R. I. Barraquer Compte, and J. L. Alio-Del Barrio, "Causes of IOL explantation in Spain," *European Journal of Ophthalmology*, vol. 5, pp. 762–768, 2012.

[126] J. L. Alio, A. B. Plaza-Puche, J. Javaloy, M. J. Ayala, L. J. Moreno, and D. P. Piero, "Comparison of a new refractive multifocal intraocular lens with an inferior segmental near add and a diffractive multifocal intraocular lens," *Ophthalmology*, vol. 119, no. 3, pp. 555–563, 2012.

[127] B. Cochener, J. Vryghem, P. Rozot et al., "Visual and refractive outcomes after implantation of a fully diffractive trifocal lens," *Clinical Ophthalmology*, vol. 6, pp. 1421–1427, 2012.

[128] A. May, "Chronic pain may change the structure of the brain," *Pain*, vol. 137, no. 1, pp. 7–15, 2008.

[129] A. May, "Structural brain imaging: a window into chronic pain," *Neuroscientist*, vol. 17, no. 2, pp. 209–220, 2011.

[130] G. J. Menon, I. Rahman, S. J. Menon, and G. N. Dutton, "Complex visual hallucinations in the visually impaired: The Charles Bonnet Syndrome," *Survey of Ophthalmology*, vol. 48, no. 1, pp. 58–72, 2003.

[131] R. J. Teunisse, J. R. M. Cruysberg, A. Verbeek, and F. G. Zitman, "The Charles Bonnet syndrome: a large prospective study in The Netherlands. A study of the prevalence-of the Charles Bonnet syndrome and associated factors in 500 patients attending the University Department of Ophthalmology at Nijmegen," *British Journal of Psychiatry*, vol. 166, pp. 254–257, 1995.

[132] S. Holroyd, P. V. Rabins, D. Finkelstein, M. C. Nicholson, G. A. Chase, and S. C. Wisniewski, "Visual hallucinations in patients with macular degeneration," *American Journal of Psychiatry*, vol. 149, no. 12, pp. 1701–1706, 1992.

[133] G. Schultz and R. Melzack, "The Charles Bonnet syndrome: 'phantom visual images'," *Perception*, vol. 20, no. 6, pp. 809–825, 1991.

[134] C. S. H. Tan, B. A. Sabel, and K.-Y. Goh, "Visual hallucinations during visual recovery after central retinal artery occlusion," *Archives of Neurology*, vol. 63, no. 4, pp. 598–600, 2006.

PART II

METHODS AND RESULTS

Evaluating neurodaptation in the setting of cataract surgery with multifocal IOL implantation involved developing new clinical tools for visual function assessment.

We started by developing the Portuguese version of the Radner Reading Test. This test allows the measurement of reading speed, which is essential in modern life. The ability to identify single optotypes does not reflect the ability to read comfortably, and reading speed is not only an important component of quality of vision, but also of quality of life. The Radner Test is based on the concept of sentence optotypes. These sentences are created following highly defined rules, including the same number of words, same word length and word position. These standardized sentences are presented in a logarithmical scale, providing reliable, reproducible and comparable measurements of reading performance. We expected to find an improvement of reading speed when neuroadaptation is present, which indeed occurred. This work led to the original article number 2 "Development of the Portuguese version of a standardized reading test: the Radner-Coimbra Charts".

We also developed a psychophysical test for contrast detection with and without glare. This test allowed for the evaluation of the impact of glare on an important aspect of quality of vision, contrast sensitivity. Everyday vision involves identifying targets against different backgrounds, most often without a contrast of 100% (black against white). This setup was the same as the one used inside the magnetic scanner, for functional imaging, and therefore contained non-magnetic MRI compatible materials.

To investigate the association between dysphotopsia and neural responses in visual and higher level cortical regions in patients recently implanted with multifocal intraocular lenses we gathered data from the first study visit (early post-operative visit). This information led to original article number 3 "Functional magnetic resonance imaging to assess the neurobehavioral impact of dysphotopsia with multifocal intraocular lenses". This study showed, for the first time, the association between patients reported subjective difficulties and FMRI outcomes, independently of optical parameters and psychophysical performance. It also provided clues on the cortical areas involved in the neuroadaptation process to multifocal intraocular lenses.

Furthermore, we studied the relation between optical properties, population receptive fields (PRF), visual function and subjective quality of vision after cataract surgery. This work showed that optical properties of the eye influence PRF sizes. Aberrations of the visual system had a negative influence on visual cortical processing. Moreover, there was dissociation between

subjective quality of vision and pRF sizes, indicating that patients with better cortical resolution may have improved perception of dysphotic phenomena, and consequently more quality of vision complaints, in spite of the improved optical quality. Therefore, PRF sizes and properties are a promising measure to evaluate quality of vision from an objective point of view. This work led to the original manuscript number 4 "Optical properties influence visual cortical functional resolution after cataract surgery and both dissociate from perceived quality of vision", which is currently under review.

In order to discover how neuroadaptation to multifocal IOLs occurs, we performed a second evaluation of all patients at the 6th postoperative month. This work showed that neuroadaptation to multifocal IOLS takes place initially through recruitment of visual attentional and procedural learning networks. Thereafter, a form of long-term adaptation/functional plasticity occurs, leading to brain activity regularization towards a non-effort pattern. These results led to the original manuscript number 5 "Functional magnetic resonance imaging to assess neuroadaptation to multifocal intraocular lenses: a longitudinal study" which is under review at the Journal of Cataract and Refractive Surgery.

The aforementioned published articles and manuscripts can be found in the next pages.

Development of the Portuguese version of a standardized reading test: the Radner-Coimbra Charts – original article number 2

Development of the Portuguese version of a standardized reading test: the Radner-Coimbra Charts

Desenvolvimento da versão portuguesa do teste padronizado de leitura: tabelas Radner-Coimbra

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ABSTRACT

Purpose: To develop 27 short sentence optotypes for the Portuguese version of the Radner Reading Charts.

Methods: Thirty-four Portuguese sentences were constructed following the concept of the Radner Reading Charts to obtain highly comparable sentences in terms of lexical difficulty, syntactical complexity, word length, number of syllables, and position of words. A long text (106 words) at the 5th grade reading level was also tested to assess the validity of the reading speeds obtained with the short sentences. The short sentences and long text were tested in 50 volunteers with similar educational backgrounds (mean age 30.98 years ± 6.99 years, range 19-47 years). Reading speeds were measured with a stop-watch and reported as words per minute (wpm). The reading time for each of the short sentences to be selected for the chart was defined as falling within the range of the mean ± 0.40 × standard deviation (SD).

Results: The overall mean reading speed for each of the short sentences was 235.43 ± 36.39 wpm. The 27 sentences with a mean between 220.8 and 250.0 wpm (overall mean ± 0.40 × SD) were selected for construction of the reading charts. The mean reading speed for the long text was 212.42 ± 26.20 wpm. Correlation between the selected short sentences and long text was high (r=0.86). Reliability analysis yielded an overall Cronbach's alpha coefficient of 0.97.

Conclusions: The 27 short Portuguese sentences were highly comparable in terms of syntactical structure, number, position and length of words, lexical difficulty, and reading length. This reading test can overcome the limitations of the current tests for homogeneity and comparability, reducing subjectivity in the evaluation of the functional outcomes of medical and surgical ophthalmologic treatments.

Keywords: Reading; Vision tests/methods; Visual acuity; Feasibility studies

RESUMO

Objetivo: *Desenvolver 27 frases-optotipo para a versão em português das tabelas de leitura de Radner.*

Métodos: *Trinta e quatro frases em português foram elaboradas de acordo com o conceito das tabelas de leitura de Radner, de forma a obter frases-optotipo, altamente comparáveis em termos dificuldade lexical, complexidade sintática, tamanho das palavras, número de sílabas e posição das palavras. Foi também avaliado um texto longo (106 palavras) ao nível do 5º ano de escolaridade para determinar a validade dos resultados obtidos com as frases curtas. As frases curtas e o texto longo foram testados em 50 voluntários de nível acadêmico semelhante e média de idades de 30,98 anos ± 6,99 (intervalo de 19-47 anos). A velociade de leitura foi medida com cronômetro, de forma a obter o número de palavras por minuto (wpm). O intervalo válido para tempo de leitura das frases curtas foi definido como a média ± 0,40 x desvio padrão (SD). As frases mais semelhantes foram estatisticamente selecionadas para a construção das tabelas de leitura Radner-Coimbra.*

Resultados: *A velocidade média de leitura obtida com as frases curtas foi 235,43 ± 36,39 wpm. As frases com velocidade média entre 220,8 e 250,0 palavras por minuto (média ± 0,40 x SD) foram selecionadas. Vinte e sete frases cumpriram este critério. A velocidade média de leitura do texto longo foi 212,42 ± 26,20 wpm. A correlação entre as frases curtas selecionadas e o texto longo foi alta (r=0,86). A análise de fiabilidade originou um coeficiente alfa de Cronbach de 0,97.*

Conclusões: *As 27 frases em português são altamente semelhantes em termos de estrutura sintática, número, posição e comprimento das palavras, dificuldade lexical e duração da leitura. Este teste permite ultrapassar as limitações dos testes existentes em termos de homogeneidade e comparabilidade, reduzindo a subjetividade na avaliação dos resultados de terapêuticas médicas e cirúrgicas.*

Descritores: *Leitura; Testes visuais/métodos; Estudos de viabilidade*

INTRODUCTION

In modern society, the ability to read is essential for daily life. The loss of this ability has a severe impact on quality of life, with loss of independence and productivity[1-4]. There are several methods to correct presbyopia, such as reading lenses, laser treatments, and multifocal intraocular lenses. It is fundamental to have a standardized test to compare the outcomes of these options [1]. Routine single optotype distance visual acuity (VA) tests have been shown to be poor predictors of reading performance and cannot elucidate the full functional impairment of several ophthalmic diseases[2,3,5]. It is therefore becoming increasingly necessary to use methods that reproducibly measure the impact of visual disabilities on the patient's everyday life and to show that the recommended therapies successfully improve quality of life[4,6]. Modern reading charts, such as the highly standardized Radner Reading Charts, allow the simultaneous evaluation of reading acuity and reading speed and thus provide more detailed information about visual impairment than traditional near vision tests (e.g., Jaeger, Nieden, Parinaud). In addition, such reading charts provide increased accuracy[6] for the evaluation of near visual performance and have become a valuable clinical tool for pre- and postoperative assessment and for visual rehabilitation[7-12].

International standards should be applied to the evaluation of reading performance. Bailey and Lovie described a logarithmically scaled near-vision chart and suggested that it was possible to simul-

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taneously determine reading acuity and speed with single words in a row[13]. Legge et al developed the computer-based Minnesota Low-Vision Reading Test (MNread), which presents short sentences at decreasing time periods on a computer screen[14]. These sentences have then been used for the MNread cards and consist of 3 lines and 60 characters (including spaces), representing 10 standard length words of 6 characters, as given by Carver[15,16]. However, the number, length, and position of words vary considerably[14,17].

Radner et al. emphasized the importance of sentence standardization, because sentence complexity also influences reading speed[4]. Therefore, they developed and standardized highly comparable sentences in terms of lexical difficulty, syntactical complexity, word length, number of syllables, and position of words.[4] This concept of "sentence optotypes" results in optimally constant geometric proportions and minimal variation between the test items. High reliability and validity of the sentence optotypes as well as high test-retest and interchart reliability have been shown for Radner Reading Charts[4,18].

A German version of Radner Reading Charts and versions in Spanish, English, French, Dutch, Danish, Swedish, Hungarian, Italian and Turkish have already been developed[6,19-21]. Other language versions are in process. Portuguese is the fifth most spoken language in the world, and the Lusophone (Portuguese-speaking) space is estimated to have approximately 241 million people[22].

The purpose of this study was to standardize Portuguese sentence optotypes for the Portuguese version of the Radner Reading Charts (Radner-Coimbra Reading Charts), allowing the evaluation of reading parameters in Portuguese speakers, including reading acuity, reading speed, and logarithm of the minimal angle of resolution (logMAR)/logarithm of the reading acuity determination (logRAD) differences.

METHODS

Study population

The study population consisted of 50 native Portuguese-speaking volunteers with university education and a mean age of 30.98 years ± 6.99 (range, 19-47 years).

Inclusion criteria were: best corrected visual acuity of 0.0 logMAR (20/20 Snellen) or better in each eye and absence of systemic and/or ocular pathology or medications that could influence the results of the study. All volunteers took the test binocularly, with near vision properly corrected if necessary. Binocular reading acuity at 40 cm was at least 20/20 Snellen. All tests were performed at a constant luminance of 80-90 cd/m^2. The study followed the tenets of the Declaration of Helsinki. An informed consent document was reviewed and signed by all volunteers.

Design of test sentences

The sentence optotypes (Figure 1) are relative clauses, which represent the first complex but still easy readable and commonly used adult sentences.

A total of 34 sentences were developed to be as comparable as possible in terms of grammatical difficulty as well as in number (14), length, and position of words. The sentences followed the rules that have been generated for sentence optotypes of the Radner Reading Charts, with minor language-specific modifications[4].

Measurements

The 34 sentences were printed in 12-point Arial font, with a maximum of 8 on each page. The reading distance was 40 cm, and luminance was 80-90 cd/m^2. The sentences were covered with a blank piece of paper, and the volunteers were asked to uncover the sentences sequentially, reading each one aloud as quickly and accurately as possible. They were advised not to stop or repeat part of the sentence to correct mistakes. The procedure was the same for all sentences.

Os clientes escolhem as cores
de catálogos, que tinham sido
levados pelos novos pintores

As escadas do hospital estão
a escorregar, porque foram já
lavadas pela nova empregada

A menina passeia pelas ruas
na bicicleta rosa, que tinha
recebido com muita satisfação

Figure 1. Sample sentences from the 34 sentence optotypes developed and tested for the Radner-Coimbra Chart.

Reading time was measured with a stopwatch. Reading speed in words per minute (wpm) was calculated on the basis of the number of words in a sentence (14 words) and the time needed to read the sentence (14 words × 60 seconds divided by the reading time). Reading errors were noted by marking the wrong words in the sentence on a study form. Errors were counted even when immediately corrected. The criterion for selection of sentences for the chart was a reading time within the range defined by the overall mean reading time for each of the sentences ± 0.40 × SD (standard deviation). A longer text of 106 words ("A Fada Oriana") at the 5th grade reading level (ie, for 10-year-old school children) was tested for reading speed to assess the validity of the results obtained with the short sentences. The main outcome measures were reading time and number of mistakes for each sentence.

Statistical analysis

Statistical analyses were performed using SPSS for Windows (version 19.0, SPSS, Inc.). The mean ± SD of both the reading time and number of mistakes made in each sentence were calculated. The data showed a fairly symmetric unimodal distribution, so that the assumption of a normal distribution for the mean, as required for the t test, was justified (Kolmogorov-Smirnov). Correlation analyses were performed using Pearson correlation. The cut-off level for statistical significance was set at $P<0.01$, two-tailed.

RESULTS

The mean reading speed for all sentences was 235.43 ± 36.39 wpm (range, 126.5 to 389.6). The mean reading time per sentence was 3.66 ± 0.59 seconds (sec). To be selected for the reading charts, the mean time to read a sentence optotype had to be within the range of 3.42 to 3.89 sec (range calculated as 3.66 ± 0.4 × SD), with a reading speed between 220.8 to 250.0 wpm (range calculated as 235.43 ± 0.4 × SD). Of the 34 sentences tested, 27 met the reading time and speed criteria. Seven sentences (numbers 9, 13, 19, 27, 28, 33, and 34) were excluded because they were outside the prescribed range. Figure 2 shows the mean reading time for each sentence.

The mean number of reading mistakes for all sentences was 0.13 ± 0.37 words/sentence (Figure 3). The mean number of reading mistakes for the long text was 0.80 ± 0.99 words/sentence.

To assess the validity of the reading speed measurements obtained with our short sentences, we compared these reading speed results to those obtained with the long text (Figure 4). The mean reading speed

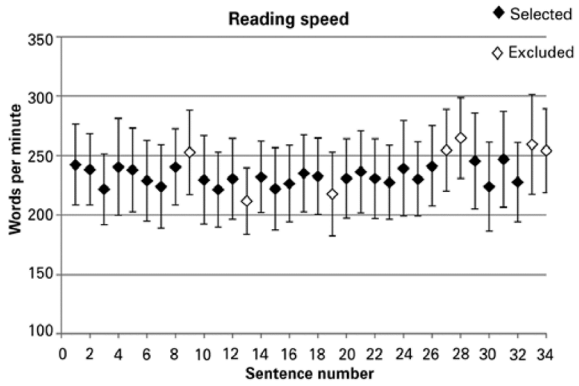

Figure 2. Mean reading speed and standard deviation for 34 sentence optotypes (overall mean reading speed: 235.43 ± 36.39 wpm). Black diamonds represent the sentences selected for the Radner-Coimbra Chart; white diamonds represent excluded sentences.

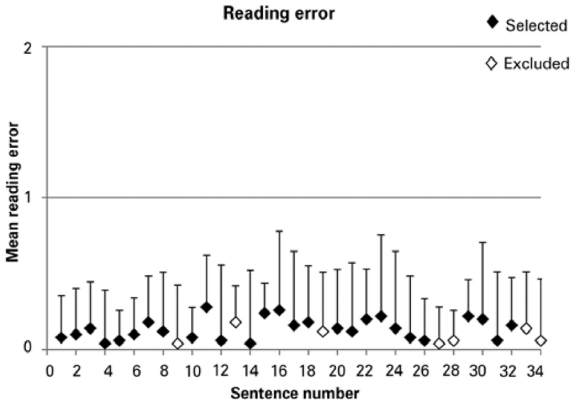

Figure 3. Mean error number and standard deviation for the 34 sentence optotypes. The mean number of reading errors was 0.13 ± 0.37 errors. Black diamonds represent the sentences selected for the Radner-Coimbra Chart; white diamonds represent excluded sentences.

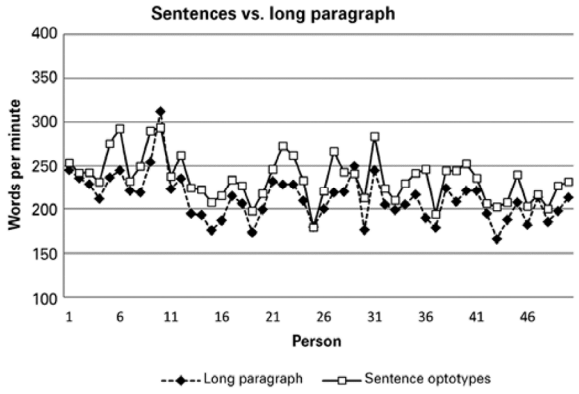

Figure 4. Reading speeds of 50 readers, comparing reading of a long paragraph (106 words; diamonds) vs. sentence optotypes (squares).

for the long text was 212.42 ± 26.20 wpm. This was lower than that for the short sentences, but the correlation between the two methods was high (r=0.86, p<0.001), thus confirming the validity of the results obtained with the short sentences.

The reliability analysis for reading speed results for the short sentence optotypes yielded an overall Cronbach's alpha coefficient of 0.98 for all 34 sentences and 0.97 for the 27 selected sentences. The coefficient of reliability for each of the 27 sentence optotypes varied from 0.62 to 0.89.

DISCUSSION

Reading is a complex task that involves not only visual sensorial input but also accurate eye movements and cognitive capacity[2,3]. Therefore, reading tests are not only different from distance acuity tests but also differ from near acuity tests using single optotypes[24]. LogMAR defines the minimal angle at which two points can be recognized as being two. Although angular resolution is a key factor in reading acuity, it is not what is evaluated when reading ability is examined. LogRAD is the reading equivalent of logMAR. For a more differentiated documentation of reading acuity, the use of logRAD is preferred. LogMAR should be used exclusively for single-optotype visual acuity testing[7].

A reading speed below 80 wpm has been found to be the lower limit for recreational, sense-capturing reading performance[25,26]. In addition, because normal newspaper print size varies from 10 to 12 points, a reading acuity of at least 0.4 logRAD is a basic requirement for reasonable reading performance[26]. A recent review of the measurement properties of reading acuity tests identified 2334 articles[74]. Of these 2334, only 20 articles had information concerning the measurement properties of the tests. Of particular note, only three reading tests, IReST, MNRead, and Radner Reading Charts, were included in these assessments[24]. Both the MNRead chart and the Radner Reading Charts meet the requirements of a logarithmically progressing print size from one sentence to another and the possibility of measuring reading speed (in wpm) and reading acuity simultaneously. The original Radner Reading Charts in German are different from other performance-reading charts like the MNRead, because Radner et al. developed the concept of sentence optotypes[4]. The MNRead used sentences that were only similar in number of lines and number of characters, not in the length and position of words. Because sentence complexity also influences reading speed, Radner et al.[4,70] focused also in the importance of sentence standardization. They therefore developed and standardized highly comparable sentences in terms of lexical difficulty, syntactical complexity, word length, and number of syllables, thus establishing sentence optotypes. This principle makes these charts superior, more reliable, and easier to standardize[3,14,19]. Radner and his co-workers also demonstrated that the Radner Reading Charts with highly comparable and standardized sentence optotypes could provide reliable, reproducible and comparable measurements of reading performance for both clinical practice and scientific investigation[4,20]. They also have shown that these charts provide highly reproducible measurements of reading acuity and speed in individuals with either no or varying degrees of visual impairment. In fact, Radner Reading Charts have been successfully used in cases with a variety of ocular pathology (e.g., cataract, macular disease, amblyopia)[2,5,12,18].

The Radner Reading Charts have been developed in several languages (e.g., German, Dutch, English, French, Spanish, Danish, Hungarian, Italian, Swedish, and Turkish). However, the original German sentences cannot be literally translated. New sentence optotypes have to be composed and tested for reliability with specific modifications to fit each particular language. Similar to other language versions which are less related to German, such as the Spanish or Italian versions, the sentence criteria for the Portuguese version had to be modified also, reflecting the typical characteristics of our

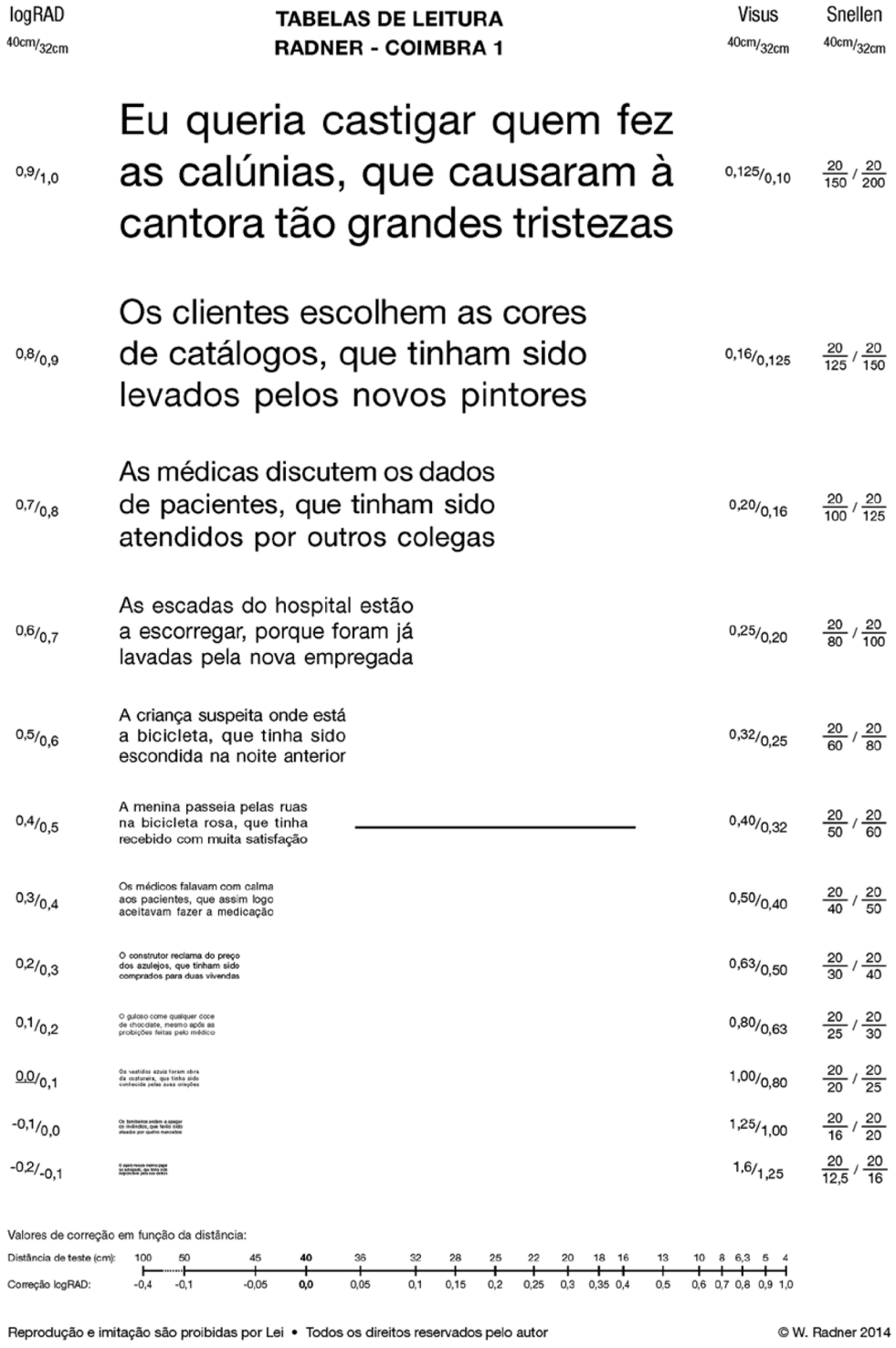

Figure 5. Example of the optotype sentences included in the Radner-Coimbra Chart.

language with regard to lexical difficulty, syntactical complexity, word length, number of syllables, and position of words. Therefore, it is important for every language to test the reliability of the Radner Reading Charts, as has been stated in other studies[6,20,21]. Although there are important dissimilarities within a language group in the way people speak the same language, written Portuguese has fewer differences. Words are essentially the same and can be read by people from different Portuguese-speaking countries, as is true for the English and Spanish versions. Furthermore, the instructions that come with the test explain that each sentence should be read word by word, so that it becomes less important if the subject performing the test would choose to say the sentence in a different way.

The sentences were created as consistently as possible, following highly defined rules, including the same number of words (14), same word length, and same word position. The typical word length and word distribution of the Portuguese language was taken into consideration. The length of a line was chosen to be between 27 and 29 characters, as in other Radner Reading Charts, because this number is used in many newspaper columns[4]. To define a set of comparable sentences as test items for the reading charts, we selected from among the initial 34 sentences the 27 with the most equivalent results. The validity of reading speed measurements obtained with the short sentences was found to correlate well with the reading speeds obtained with a long text. For example, subjects reading the long text slower also read the short sentences slower.

The test psychology and the psychological backgrounds behind the Portuguese version follow the ones originally applied in the German version. The principles and methods for sentence selection remain consistent between all languages.

Thus, reading speed measurements with our 27 short Portuguese sentence optotypes provided a valid measure of reading performance. These 27 sentences optotypes were then used for the development of the Portuguese version of the Radner Reading Charts.

In the Radner-Coimbra Reading Charts, the standardized sentence optotypes are presented in logarithmical scaling (logRAD format) in accordance with international standards in order to maintain constant geometrical proportion at all distances and limit changes in reading speed mainly to the print size (Figure 5).

In conclusion, a new version of the Radner Reading Charts in Portuguese (Radner-Coimbra Charts) was developed. The development of standardized reading charts in Portuguese for the simultaneous determination of reading acuity and reading speed in the same examination is a refinement in the diagnosis of reading performance in Portuguese speaking patients, allowing adherence to international standards for clinical research and potentially improving diagnosis in daily practice.

REFERENCES

1. Rosa AM, Loureiro Silva MF, Lobo C, Mira JB, Farinha CL, Povoa JA, et al. Comparison of visual function after bilateral implantation of inferior sector-shaped near-addition and diffractive-refractive multifocal IOLs. J Cataract Refract Surg. 2013;39(11):1653-9.
2. Elliott DB, Hurst MA, Weatherill J. Comparing clinical tests of visual function in cataract with the patient's perceived visual disability. Eye (Lond). 1990;4(Pt 5):712-7.
3. Legge GE, Ross JA, Isenberg LM, LaMay JM. Psychophysics of reading. Clinical predictors of low-vision reading speed. Invest Ophthalmol Vis Sci. 1992;33(3):677-87.
4. Radner W, Obermayer W, Richter-Mueksch S, Willinger U, Velikay-Parel M, Eisenwort B. The validity and reliability of short German sentences for measuring reading speed. Graefes Arch Clin Exp Ophthalmol. 2002;240(6):461-7.
5. Richter-Mueksch S, Stur M, Stifter E, Radner W. Differences in reading performance of patients with Drusen maculopathy and subretinal fibrosis after CNV. Graefes Arch Clin Exp Ophthalmol. 2006;244(2):154-62.
6. Alio JL, Radner W, Plaza-Puche AB, Ortiz D, Neipp MC, Quiles MJ, et al. Design of short Spanish sentences for measuring reading performance: Radner-Vissum test. J Cataract Refract Surg. 2008;34(4):638-42.
7. Richter-Mueksch S, Weghaupt H, Skorpik C, Velikay-Parel M, Radner W. Reading performance with a refractive multifocal and a diffractive bifocal intraocular lens. J Cataract Refract Surg. 2002;28(11):1957-63.
8. Burggraaff MC, van Nispen RM, Hoek S, Knol DL, van Rens GH. Feasibility of the Radner Reading Charts in low-vision patients. Graefes Arch Clin Exp Ophthalmol. 2010; 248(11):1631-7.
9. Richter-Mueksch S, Kaminski S, Kuchar A, Stifter E, Velikay-Parel M, Radner W. Influence of laser in situ keratomileusis and laser epithelial keratectomy on patients' reading performance. J Cataract Refract Surg. 2005;31(8):1544-8.
10. Hutz WW, Eckhardt HB, Rohrig B, Grolmus R. Reading ability with 3 multifocal intraocular lens models. J Cataract Refract Surg. 2006;32(12):2015-21.
11. Stifter E, Burggasser G, Hirmann E, Thaler A, Radner W. Evaluating reading acuity and speed in children with microstrabismic amblyopia using a standardized reading chart system. Graefes Arch Clin Exp Ophthalmol. 2005;243(12):1228-35.
12. Stifter E, Weghaupt H, Benesch T, Thaler A, Radner W. Discriminative power of reading tests to differentiate visual impairment caused by cataract and age-related macular degeneration. J Cataract Refract Surg. 2005;31(11):2111-9.
13. Bailey IL, Lovie JE. The design and use of a new near-vision chart. Am J Optom Physiol Opt. 1980;57(6):378-87.
14. Legge GE, Ross JA, Luebker A, LaMay JM. Psychophysics of reading. VIII. The Minnesota Low-Vision Reading Test. Optom Vis Sci. 1989;66(12):843-53.
15. Carver RP. Reading rate: a review of research and theory. San Diego: Academic Press; 1990.
16. Castro CT, Kallie CS, Salomao SR. [Development and validation of the MNREAD reading acuity chart in Portuguese]. Arq Bras Oftalmol. 2005;68(6):777-83. Portuguese.
17. Messias A, Velasco e Cruz AA, Schallenmuller SJ, Trauzettel-Klosinski S. [New standardized texts in Brazilian Portuguese to assess reading speed--comparison with four European languages]. Arq Bras Oftalmol. 2008;71(4):553-8. Portuguese.
18. Stifter E, Konig F, Lang T, Bauer P, Richter-Muksch S, Velikay-Parel M, et al. Reliability of a standardized reading chart system: variance component analysis, test-retest and inter-chart reliability. Graefes Arch Clin Exp Ophthalmol. 2004;242(1):31-9.
19. Maaijwee K, Mulder P, Radner W, Van Meurs JC. Reliability testing of the Dutch version of the Radner Reading Charts. Optom Vis Sci. 2008;85(5):353-8.
20. Radner W, Diendorfer G. English sentence optotypes for measuring reading acuity and speed--the English version of the Radner Reading Charts. Graefes Arch Clin Exp Ophthalmol. 2014;252(8):1297-303.
21. Calossi A, Boccardo L, Fossetti A, Radner W. Design of short Italian sentences to assess near vision performance. J Optom. 2014;7(4):203-9.
22. Utah TUo. Portuguese & Brazilian Studies 2015 [20th March 2015].
23. Latham K, Whitaker D. A comparison of word recognition and reading performance in foveal and peripheral vision. Vision Res. 1996;36(17):2665-74.
24. Brussee T, van Nispen RM, van Rens GH. Measurement properties of continuous text reading performance tests. Ophthalmic Physiol Opt. 2014;34(6):636-57.
25. Rubin GS, West SK, Munoz B, Bandeen-Roche K, Zeger S, Schein O, et al. A comprehensive assessment of visual impairment in a population of older Americans. The SEE Study. Salisbury Eye Evaluation Project. Invest Ophthalmol Vis Sci. 1997;38(3):557-68.
26. West SK, Munoz B, Rubin GS, Schein OD, Bandeen-Roche K, Zeger S, et al. Function and visual impairment in a population-based study of older adults. The SEE project. Salisbury Eye Evaluation. Invest Ophthalmol Vis Sci. 1997;38(1):72-82.

Functional magnetic resonance imaging to assess the neurobehavioral impact of dysphotopsia with multifocal intraocular lenses – original article number 3

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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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Ophthalmology Volume ■, Number ■, Month 2017

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 spherico-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).[21] 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).[22] 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.[23] 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/m^2). 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/m^2 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[24] 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[25] 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. Each visual stimulus was present during 700 ms, and between each event, there was a baseline fixation period during which the subject answered if he/she saw the stimulus or not by pressing 1 of 2 keys on a joystick (forced-choice paradigm, to ensure the subject's attention). The baseline fixation periods lasted 3300 ms, 5300 ms, or 7300 ms, occurring randomly. As in the psychophysical assessment, patients wore no spectacle correction and controls had their usual prescription, inserted in a nonmagnetic trial frame.

Magnetic Resonance Imaging Data Acquisition. The MRI acquisitions were performed at the Brain Imaging Network facilities, on a 3-Tesla Magneton TIM Trio scanner (Siemens, Munich, Germany) equipped with a 32-Channel Head Coil (Siemens).

The anatomic images were acquired using a standard T1-weighted gradient echo pulse sequence (echo time = 3.42 ms, repetition time = 2.530 ms, flip angle: 7°, inversion time = 1.100 ms, 176 slices with voxel size 1×1×1 mm, field of view [FOV] 256 mm). Functional images were acquired using a T2*-weighted gradient echo echo-planar imaging with echo time = 30 ms, repetition time = 2000 ms, flip angle: 90°, 29 interleaved slices with voxel size 2×2×2 mm, FOV 256 mm, for the block design paradigm; and echo time = 30 ms, repetition time = 2000 ms, flip angle: 90°, 35 interleaved slices with voxel size 3×3×3 mm, FOV 256 mm, for the event-related design paradigm. In the block design stimulation, the slices were orthogonal to the calcarine sulcus with no gap, whereas in the event-related stimulation the slices were oriented to obtain whole brain coverage. Visual stimuli were displayed on an LCD (Inroom Viewing Device, Nordic NeuroLab, Bergen, Norway), positioned at the back of the scanner and viewed through a mirror attached to the head coil.

Magnetic Resonance Imaging Data Analysis. Anatomic and functional data processing and retinotopic mapping were performed using the BrainVoyager QX software (version 2.8.2, Brain Innovation B.V., Maastricht, The Netherlands).

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.[26] 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.[27] These ROIs were mapped back into the brain volume space and

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Ophthalmology Volume ■, Number ■, Month 2017

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).[28] 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.[29] 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–Wilk 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).[30] According to Desmond and Glover,[31] in fMRI studies a minimum of 12 subjects are needed to ensure 80% power at an alpha = 0.05.[31] 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 multisubject 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

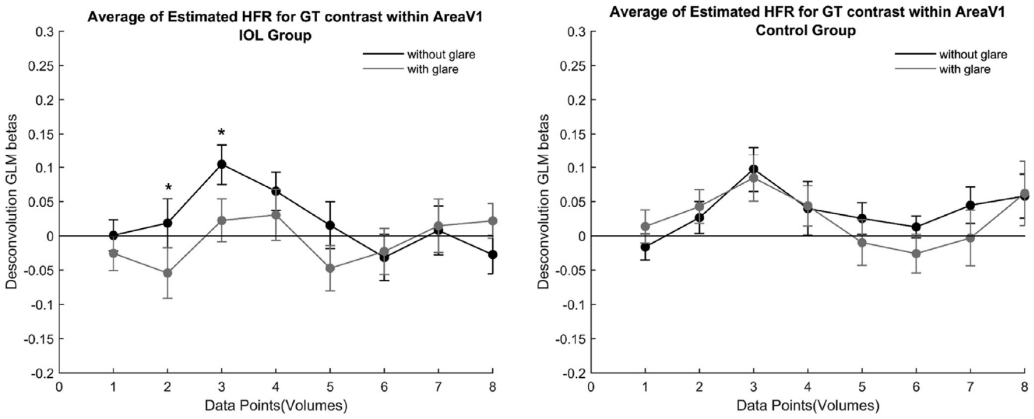

Figure 1. Hemodynamic function response curves, displaying the blood oxygen level dependent (BOLD) signal (beta values) within the primary visual cortex as a function of time (each volume corresponding to 2 seconds) in multifocal patients and control subjects. After stimuli presentation, the BOLD signals peaks because of the compensatory increase in oxygenated hemoglobin (β max). Afterward, it declines to a minimum before returning to baseline. Glare decreases BOLD signal in the primary visual cortex (V1) of patients who underwent surgery recently. The magnitude of the differences in β max between glare and no glare conditions is greater for patients than for controls (effect sizes are 0.49 and 0.10, respectively). Both β max and area under the curve for threshold contrast events under glare show a significant decrease in recently operated patients. No significant change is observed in controls (*right*). *$P < 0.05$, Wilcoxon rank-sum test. GLM = general linear model; GT = glare threshold; HFR = hemodynamic function response; IOL = intraocular lens; SEM = standard error mean.

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.[3–6,10] Even with the new

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Ophthalmology Volume ■, Number ■, Month 2017

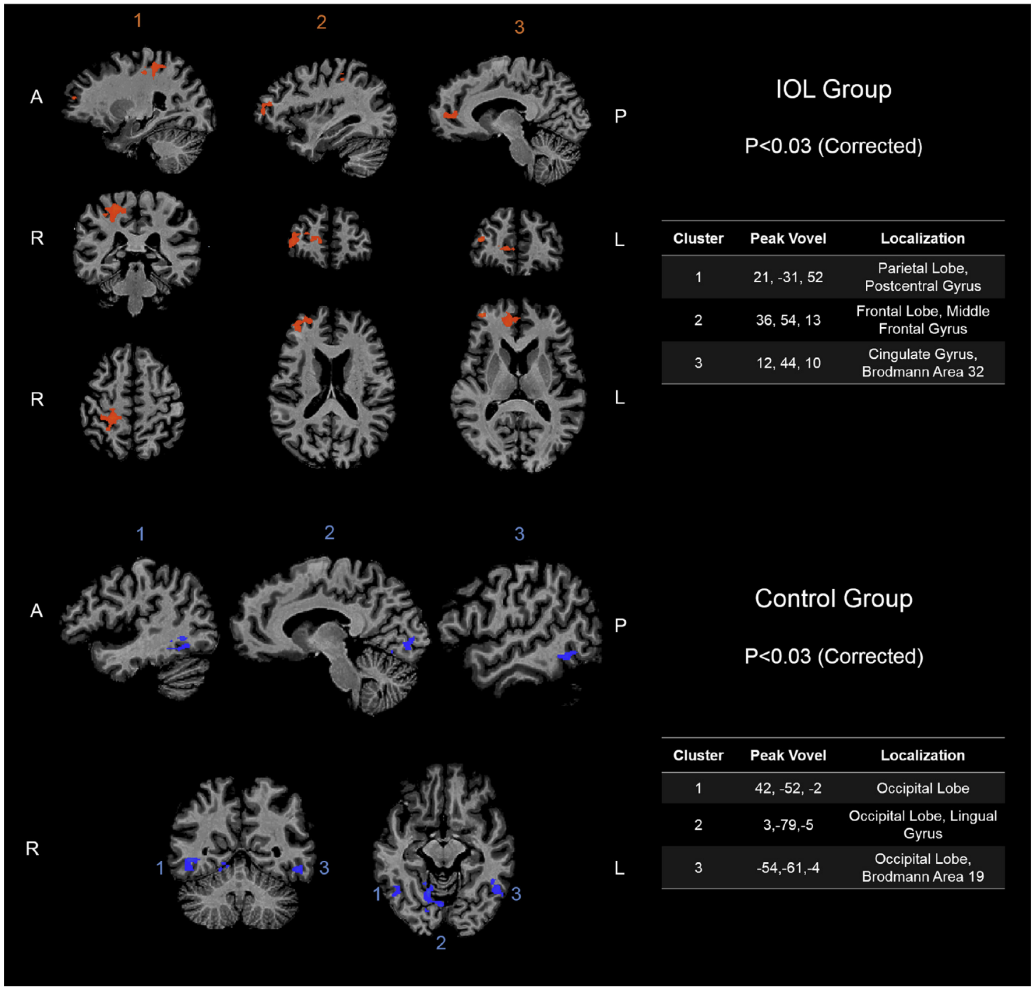

Figure 2. Top: When patients are asked to discriminate a threshold stimulus under glare in comparison with a 2.5 higher contrast stimulus without glare, there is activation of cortical areas involved in attention (parietal and frontal lobes) and learning (anterior cingulate gyrus). **Bottom**: Under the same circumstances, controls show relative deactivations in the occipital lobe, but no significant effort, attention, or learning cortical areas engagement. IOL = intraocular lens.

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,

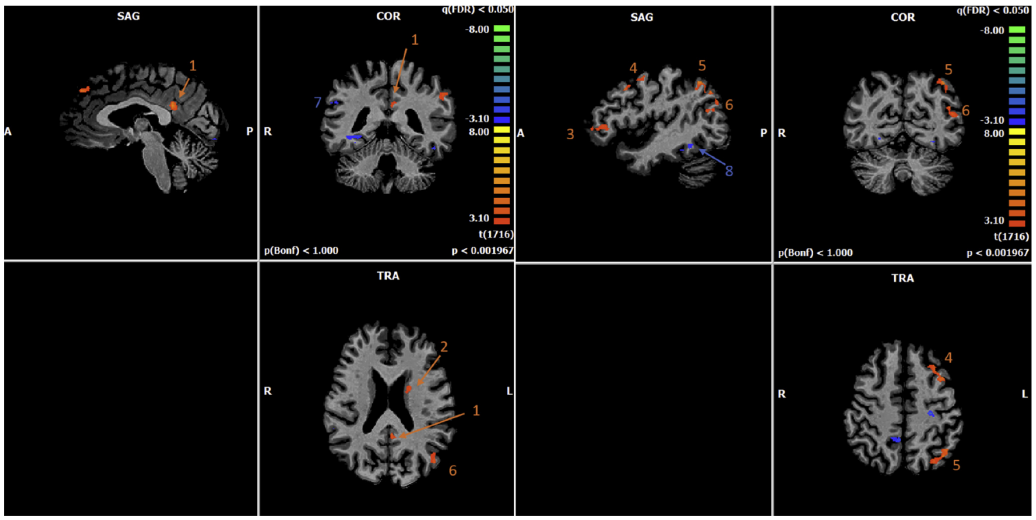

Figure 3. Patients and controls were presented a low-contrast stimulus (near threshold). Cortical areas that were relatively more activated in patients were located in the anterior cingulate gyrus (1), caudate body (2), middle frontal gyrus (3 and 4), superior parietal lobule (5), and middle occipital 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.

because neural adaptation to multifocality may vary among patients.[10] 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.[34] 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.[35] 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.

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

	QoV Score (Average, Median)	
Subscale	*Patients (n = 30)*	*Controls (n = 15)*
Frequency	45.6, 45	24.5, 25
Severity	38.6, 39	21.6, 22
Bothersome	30.7, 34	18.4, 14

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

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.[17] 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 with higher-

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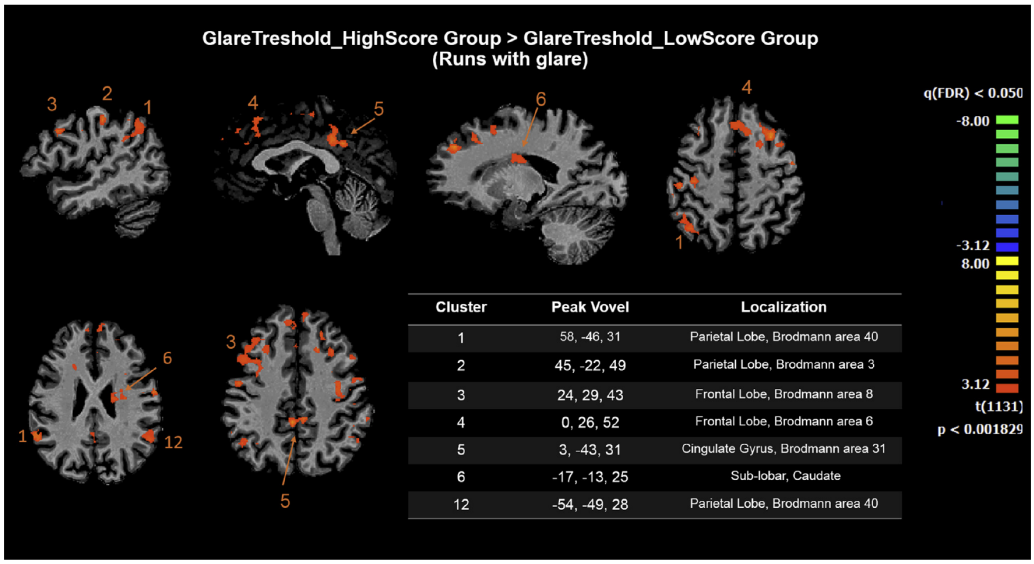

Figure 4. Patients feeling more bothered by dysphotic symptoms were compared with those less bothered when both groups were presented with a low contrast stimulus under glare. The high score group (more bothered) showed significantly increased activity in several regions in the frontal and parietal lobes, as well as cingulate gyrus and caudate activations (q [false discovery rate] <0.05).

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,[36] learning,[37] and memory.[38] The anterior cingulate cortex appears to play a crucial role in initiation, motivation, and goal-directed behaviors,[38] 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.[39]

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

Total RMS [mean (μm) ± SD]	0.42±0.17
Higher-order RMS [mean (μm) ± SD]	0.16±0.08
Average MTF height (mean ± SD)	0.31±0.09
MTF for 10 cpd spatial frequencies (mean ± SD)	0.29±0.14
Strehl ratio (mean ± SD)	0.07±0.05
Visual acuity (mean ± SD)	
UCDVA (logMAR)	0.06±0.11
CDVA (logMAR)	−0.01±0.09
DCNVA (logRAD)	0.13±0.11
CNVA (logRAD)	0.05±0.08
UCNVA (logRAD)	0.08±0.12
DCIVA (logMAR)	0.30±0.11
UCIVA (logMAR)	0.20±0.1

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; UCIVA = uncorrected intermediate 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.

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.[40] In other words, the caudate region plays a fulcral role in the planning and execution of strategies to attain complex/difficult goals. It has been shown that increasing the

difficulty of a problem to be solved results in increased activity in the caudate nucleus.[41] 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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References

1. Rosa AM, Loureiro Silva MF, Lobo C, et al. Comparison of visual function after bilateral implantation of inferior sector-shaped near-addition and diffractive-refractive multifocal IOLs. *J Cataract Refract Surg*. 2013;39:1653-1659.
2. Nijkamp MD, Dolders MG, de Brabander J, et al. Effectiveness of multifocal intraocular lenses to correct presbyopia after cataract surgery: a randomized controlled trial. *Ophthalmology*. 2004;111:1832-1839.
3. Kinard K, Jarstad A, Olson RJ. Correlation of visual quality with satisfaction and function in a normal cohort of pseudophakic patients. *J Cataract Refract Surg*. 2013;39:590-597.
4. de Vries NE, Webers CA, Touwslager WR, et al. Dissatisfaction after implantation of multifocal intraocular lenses. *J Cataract Refract Surg*. 2011;37:859-865.
5. Wilkins MR, Allan BD, Rubin GS, et al. Randomized trial of multifocal intraocular lenses versus monovision after bilateral cataract surgery. *Ophthalmology*. 2013;120:2449-2455.e1.
6. Woodward MA, Randleman JB, Stulting RD. Dissatisfaction after multifocal intraocular lens implantation. *J Cataract Refract Surg*. 2009;35:992-997.
7. Welch NR, Gregori N, Zabriskie N, Olson RJ. Satisfaction and dysphotopsia in the pseudophakic patient. *Can J Ophthalmol*. 2010;45:140-143.
8. Holladay JT, Zhao H, Reisin CR. Negative dysphotopsia: the enigmatic penumbra. *J Cataract Refract Surg*. 2012;38:1251-1265.
9. Calladine D, Evans JR, Shah S, Leyland M. Multifocal versus monofocal intraocular lenses after cataract extraction. *Cochrane Database Syst Rev*. 2012;9:CD003169.
10. Rosen E, Alio JL, Dick HB, et al. Efficacy and safety of multifocal intraocular lenses following cataract and refractive lens exchange: metaanalysis of peer-reviewed publications. *J Cataract Refract Surg*. 2016;42:310-328.
11. McAlinden C, Skiadaresi E, Khadka J, Pesudovs K. Pupil size and LASIK. *Ophthalmology*. 2012;119:1715-1717.
12. McAlinden C, Khadka J, Pesudovs K, Skiadaresi E. Subjective quality of vision. *J Refract Surg*. 2012;28:314.
13. Braga-Mele R, Chang D, Dewey S, et al. Multifocal intraocular lenses: relative indications and contraindications for implantation. *J Cataract Refract Surg*. 2014;40:313-322.
14. Alio JL, Plaza-Puche AB, Javaloy J, et al. Comparison of a new refractive multifocal intraocular lens with an inferior segmental near add and a diffractive multifocal intraocular lens. *Ophthalmology*. 2012;119:555-563.
15. Miki A, Haselgrove JC, Liu GT. Functional magnetic resonance imaging and its clinical utility in patients with visual disturbances. *Surv Ophthalmol*. 2002;47:562-579.
16. Malecaze FJ, Boulanouar KA, Demonet JF, et al. Abnormal activation in the visual cortex after corneal refractive surgery for myopia: demonstration by functional magnetic resonance imaging. *Ophthalmology*. 2001;108:2213-2218.
17. Martins Rosa A, Silva MF, Ferreira S, et al. Plasticity in the human visual cortex: an ophthalmology-based perspective. *Biomed Res Int*. 2013;2013:568354.
18. Vuori E, Vanni S, Henriksson L, et al. Refractive surgery in anisometropic adult patients induce plastic changes in primary visual cortex. *Acta Ophthalmol*. 2012;90:669-676.
19. Baker CI, Peli E, Knouf N, Kanwisher NG. Reorganization of visual processing in macular degeneration. *J Neurosci*. 2005;25:614-618.
20. Rosa AM, Farinha CL, Radner W, et al. Development of the Portuguese version of a standardized reading test: the Radner-Coimbra Charts. *Arq Bras Oftalmol*. 2016;79:238-242.
21. McAlinden C, Pesudovs K, Moore JE. The development of an instrument to measure quality of vision: the Quality of Vision (QoV) questionnaire. *Invest Ophthalmol Vis Sci*. 2010;51:5537-5545.
22. McAlinden C, Skiadaresi E, Gatinel D, et al. The Quality of Vision questionnaire: subscale interchangeability. *Optom Vis Sci*. 2013;90:760-764.

23. Brainard DH. The Psychophysics Toolbox. *Spat Vis*. 1997;10:433-436.
24. Zychaluk K, Foster DH. Model-free estimation of the psychometric function. *Atten Percept Psychophys*. 2009;71:1414-1425.
25. Dumoulin SO, Wandell BA. Population receptive field estimates in human visual cortex. *Neuroimage*. 2008;39:647-660.
26. Kriegeskorte N, Goebel R. An efficient algorithm for topologically correct segmentation of the cortical sheet in anatomical MR volumes. *Neuroimage*. 2001;14:329-346.
27. Binda P, Thomas JM, Boynton GM, Fine I. Minimizing biases in estimating the reorganization of human visual areas with BOLD retinotopic mapping. *J Vis*. 2013;13:13.
28. Serences JT. A comparison of methods for characterizing the event-related BOLD timeseries in rapid fMRI. *Neuroimage*. 2004;21:1690-1700.
29. Beckmann CF, Jenkinson M, Smith SM. General multilevel linear modeling for group analysis in FMRI. *Neuroimage*. 2003;20:1052-1063.
30. Bhaumik DK, Roy A, Lazar NA, et al. Hypothesis testing, power and sample size determination for between group comparisons in fMRI experiments. *Stat Methodol*. 2009;6:133-146.
31. Desmond JE, Glover GH. Estimating sample size in functional MRI (fMRI) neuroimaging studies: statistical power analyses. *J Neurosci Methods*. 2002;118:115-128.
32. Mendicute J, Kapp A, Levy P, et al. Evaluation of visual outcomes and patient satisfaction after implantation of a diffractive trifocal intraocular lens. *J Cataract Refract Surg*. 2016;42:203-210.
33. Liang B, Liu R, Dai Y, et al. Effects of ocular aberrations on contrast detection in noise. *J Vis*. 2012;12(8).
34. Fiorentini A, Maffei L, Sandini G. The role of high spatial frequencies in face perception. *Perception*. 2013;42:1151-1157.
35. Mainster MA, Turner PL. Glare's causes, consequences, and clinical challenges after a century of ophthalmic study. *Am J Ophthalmol*. 2012;153:587-593.
36. Halari R, Simic M, Pariante CM, et al. Reduced activation in lateral prefrontal cortex and anterior cingulate during attention and cognitive control functions in medication-naive adolescents with depression compared to controls. *J Child Psychol Psychiatry*. 2009;50:307-316.
37. Sutherland RJ, Whishaw IQ, Kolb B. Contributions of cingulate cortex to two forms of spatial learning and memory. *J Neurosci*. 1988;8:1863-1872.
38. Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behaviour. *Brain*. 1995;118(Pt 1):279-306.
39. Imamoglu F, Heinzle J, Imfeld A, Haynes JD. Activity in high-level brain regions reflects visibility of low-level stimuli. *Neuroimage*. 2014;102(Pt 2):688-694.
40. Grahn JA, Parkinson JA, Owen AM. The cognitive functions of the caudate nucleus. *Prog Neurobiol*. 2008;86:141-155.
41. Dagher A, Owen AM, Boecker H, Brooks DJ. Mapping the network for planning: a correlational PET activation study with the Tower of London task. *Brain*. 1999;122(Pt 10):1973-1987.

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Author Contributions:

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Data collection: Rosa, Miranda

Analysis and interpretation: Rosa, Miranda, Patrício, McAlinden, Silva, Murta, Castelo-Branco

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Overall responsibility: Rosa, Miranda, Patrício, McAlinden, Silva, Murta, Castelo-Branco

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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Optical properties influence visual cortical resolution after cataract surgery and dissociate from perceived quality of vision – original article number 4 (under review)

Optical properties influence visual cortical functional resolution after cataract surgery and both dissociate from perceived quality of vision

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Abstract

Purpose. To investigate the relation between optical properties, population receptive fields (pRF), visual function and subjective quality of vision after cataract surgery.

Methods. The study includes 30 patients who had recently undergone bilateral sequential cataract surgery. We used functional magnetic resonance imaging and pRF modelling methods to assess pRF sizes across visual cortical regions (V1-V3). Subjects also performed a complete ophthalmological and psychophysical examination and answered a quality of vision questionnaire.

Results. Subjects with worse optical properties had larger pRF sizes. In addition, analysis in the primary visual cortex revealed significantly larger mean pRF sizes for operated subjects with worse contrast sensitivity (p=0.038). In contrast, patients who were more bothered by dysphotic symptoms presented surprisingly lower pRF size fitting interception (p=0.012) and pRF size fitting slopes (p=0.020), suggesting a dissociation between objective quality of vision and subjective reports.

Conclusions. Optical properties of the eye influence PRF sizes. Aberrations of the visual system have a negative influence on visual cortical processing. Moreover, there is dissociation between subjective quality of vision and pRF sizes, indicating that patients with better cortical resolution may have improved perception of dysphotic phenomena, and consequently more quality of vision complaints, in spite of the improved optical quality. PRF sizes and properties are a valuable and promising quantitative measure to evaluate quality of vision from an objective point of view.

Introduction

Topographic mapping of the human visual cortex (cortical retinotopy) using non-invasive neuroimaging techniques plays a relevant role in understanding visual function, and can be achieved by using functional magnetic resonance imaging (fMRI).[1–3] Several

efforts have been made to identify and efficiently characterize properties of the human visual field maps. Engel et al. (1994) introduced a phase-encoded method to characterize the activity of the human visual cortex in both health and disease, taking advantage of the retinotopic configuration of the visual system [4–8].

More recently, a population receptive field (pRF) modelling approach was proposed by Dumoulin & Wandel (2008). By incorporating an explicit model of neural responses preferences, pRF modelling provides information about the receptive field properties underlying fMRI responses. A pRF can be seen as the aggregate receptive field of the many neurons within an fMRI voxel that respond to stimulation of a particular retinal location.[10,11] Smaller pRFs reflect more fine-tuned visual processing, effectively increasing the spatial resolution of the visual system, while large pRFs reflect a coarser neural representation of visual space [18,19] PRF sizes are influenced by eccentricity, with the smallest pRFs (reflecting underlying single-neuron receptive fields) being present in the neural representation of the central visual field, where visual acuity is greatest.[9,20,21] PRFs also vary hierarchically between visual areas, having smaller sizes in the primary visual cortex (V1).

PRF properties have been used to evaluate adaptive changes in the human brain resulting from diseases, trauma and degeneration, with pRF changes mirroring changes in visual function.[12–18] PRF properties might also be used to help us understand how the optical properties of the eye influence the functional response properties of the visual cortex.

Recent studies suggested an association between perceptual acuity and neuronal population tuning in the primary and secondary visual cortex [18] and between acuity thresholds and cortical magnification in V1.[22] However, although optical parameters of the eye influence the processing of visual information, their impact on pRF sizes remains unclear.

This study aims to evaluate the association between pRF size, visual function (including visual acuity), subjectively perceived quality of vision and optical properties of

the eye, including wavefront analysis. This approach is relevant to understand how the human brain adapts to the imperfections of each visual system (eye).[23–26] Therefore, we opted to study patients with recent cataract surgery and, consequently, with a changed optical visual system and no established long-term adaptation.

Materials and methods

Subjects

This cross-sectional study included 30 patients aged less than 75 years, who received bilaterally diffractive bifocal intraocular lenses. Inclusion criteria comprised: no surgical complications, pre-operative sphere inferior to 6 diopters (D) in magnitude in either eye, regular topography with less than 1.5 D of astigmatism, no history of previous corneal or intraocular surgery, absence of other ocular comorbidities and of metallic foreign bodies. Non-toric multifocal lenses (Acrysof Restor SN6AD1 IOL, Alcon Surgical, with a +3.00 addition) were implanted binocularly, with approximately a 1-week interval.

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 subjects were given an information letter, followed by the clarification of any questions that might have arisen. All participants were adequately informed and signed the informed consent form.

Ophthalmological examination

At the third week after the second eye surgery, a complete ophthalmological examination was performed, comprising uncorrected and corrected distance and near visual acuities, distance-corrected near visual acuity, uncorrected and distance-corrected intermediate visual acuity, slit-lamp examination, tonometry and fundoscopy.

Distance visual acuity was measured using ETDRS charts and near visual acuity using the Portuguese version of the Radner test (Radner-Coimbra Reading Charts[27]). All measurements were performed under photopic conditions (80cd/m^2).

Optical properties

We used the iTrace (version 6.0.1, Tracey Technologies), which combines an aberrometer with corneal topography, to obtain total ocular and internal aberrations, Strehl ratio and MTF. The best quality scan of the three manual measurements at 4 mm (after pupil dilation) was selected for further analysis. Total RMS, RMS of HOAs from 3rd- to 5th-order Zernike coefficients, average MTF height (MTF_h), MTF at 10 cycles per degree (cpd) and Strehl ratio were registered for corneal, internal and total ocular optics. Values were extracted without spherico-cylindrical correction.

Quality of vision questionnaire

Using the 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, distance or depth perception difficulties) in three subscales (frequency, severity, and bothersome).[28] Raw questionnaire data were Rasch-scaled to provide interval-level measurement properties.[29]

Magnetic Resonance Imaging

Stimulus presentation and apparatus

We generated our visual field mapping stimulus in MATLAB (Version R2014b), using the Psychophysics Toolbox[30]. The visual stimulus was displayed on a 32 inches. NNL LCD monitor (InroomViewingDevice, NordicNeuroLab, Norway) at a resolution of 1920 x 1080 pixels positioned at the end of the magnet bore of the scanner and viewed

through a mirror attached to a head coil. The display was 70x39.5 cm and the viewing distance was 156.5 cm, so it subtended a 22.21°x14.38° visual angle.

Simultaneous Bars Stimuli

We developed a new visual stimulus to increase mapping efficiency and fMRI response amplitudes. It consisted of two perpendicular bars that crossed the display in different phases and orthogonal directions. This design has previously increased mapping efficiency,[31] although here we used horizontal and vertical bars, subtending 1.80º and 1.57º of visual angle, respectively [9,19,31,32], rather than wedges and rings.[9,19] Within these bar apertures, we displayed a coloured checkerboard pattern, with the colour of each square flickering between randomly chosen RGB colour values on each frame.[33] The horizontal bars moved vertically across the display in 18 equally spaced steps, while the vertical bars moved horizontally across the display in 24 equally spaced steps. Each bar position was presented for two seconds (s) to synchronize with the fMRI volume of acquisition.

The high-contrast horizontal and vertical bars each crossed the display repeatedly, with the horizontal bars taking 36 s to complete a full cycle and the vertical bars taking 48 s (figure 1). These asynchronous cycles allow pRF modelling to determine pRF positions in both dimensions simultaneously.[31] After 144 s, a 30 s period of mean luminance (zero-contrast) was displayed, providing a 'blank' period that allows pRF models to determine the baseline fMRI response amplitude.[9,19,32]

In the first 144 s of each scanning run, the horizontal bars travelled downwards and the vertical bars travelled leftwards. After the blank period, both horizontal and vertical bars travelled in the opposite direction.

Participants were instructed to fixate a point in the centre of the visual stimulus. The colours changed between red and green at random intervals, from 1.5 s to 6 s. To

ensure attention and fixation, participants pressed a button each time they detected a colour change.

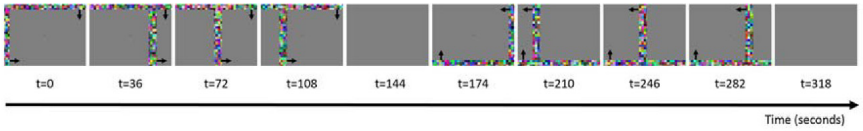

Figure 1. Illustration of Simultaneous Bars Mapping Stimuli. The arrows indicated the motion direction of the bars.

Data acquisition

Magnetic resonance images (MRI) were acquired on a 3-Tesla Magneton TIM Trio scanner equipped with a 32-Channel Head Coil (Siemens, Erlangen, Germany).

Two high-resolution 3D anatomical MPRAGE (magnetization prepared rapid-acquisition gradient echo) images were acquired using a standard T_1-weightened gradient eco (GE) pulse sequence (field of view (FOV) = 256 x 256 mm, 176 slices, voxel size 1x1 x1mm, repetition time (TR)=2.530 ms, echo time (TE)=3.42 ms, inversion time (TI)=1.100ms, 7º flip angle).

Functional MRI were recorded using a T_2-weighted GE echo-planar imaging (EPI) sequence over 3 runs at an isotropic resolution of 2 mm (FOV 256 x 256 mm), with 29 interleaved slices oriented orthogonally to the calcarine sulcus with no gap. TE was 30 ms, TR was 2000 ms and flip angle was 90º. Each functional run was acquired using 180 time frames (360 s).

Anatomical and Functional preprocessing

All image data was processed and analysed using the BrainVoyager QX software (version 2.8.2, Brain Innovation B.V., Maastricht, The Netherlands).

Anatomical images underwent brain extraction and intensity normalization to reduce artefacts and inhomogeneity caused by the magnetic field.[34] The two anatomical data sets were then aligned to each other and averaged to improve the signal-to-noise ratio.[35] The resulting images were converted to the Talairach reference system.[36] Thereafter, white matter was segmented using an automatic segmentation routine[37] and small manual adjustments were made. Mesh representations of each hemisphere were then created.[38,39]

The first six volumes of each experimental run were excluded from the analysis due to early magnetization transients. Functional data pre-processing included 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. All functional volumes were corrected for motion within and between scan. As the head motion was minimal (≤ 2mm in any direction) no block was excluded.

The pre-processed functional runs were co-registered with each subject's structural scan in Tailarach space and then averaged across scans.

Population Receptive Field modelling and analysis

PRF models were estimated from BOLD responses to the simultaneous bars moving stimuli using a model-driven approach developed by Dumoulin & Wandell (2008) and recently implemented in BrainVoyager QX (2013). Briefly, the pRF approach estimates a neural response model, for each voxel, that best explains the cortical visual field responses to a wide range of stimulus position.[9,19]

First, we generated a binary stimuli frame containing detailed information about the sequence of visual field positions covered by the bars in the stimulus. Then, a large set of candidate pRF models were used to sample the frame and calculate at each time point (frame) a neural response strength that depends on the overlap between the stimulus and the Gaussian model.[40] These candidate neural response time courses were each convolved with a canonical hemodynamic response function to predict, for each set of candidate pRF parameters, the BOLD response time course that the stimulus would yield. The candidate response predictions were each compared against the measured response of every voxel. The pRF model that most closely fits the measured response of each voxel was chosen, giving the goodness of model fit (variance explained), the pRF size (σ) and preferred position (x and y). These position preferences were converted to preferred eccentricity and polar angle to delineate each visual field map.

The resulting parameter maps were projected on the inflated meshes. Retinotopic areas were manually drawn for each subject based on polar angle and eccentricity maps (figure 2).[10,41–43] Although we could identify visual field maps, we restricted our analysis to the primary visual cortex.

All the voxels with a poor pRF model fit, i.e. with less than 30% of the variance explained, were removed from the analysis, as well as the voxels outside of the delineated region of interest (ROI). We also excluded voxels with pRF eccentricities bellow 0.5º since this part of the visual field is difficult to accurately map, and those outside of the limits of the central vision (5º of eccentricity),[44].

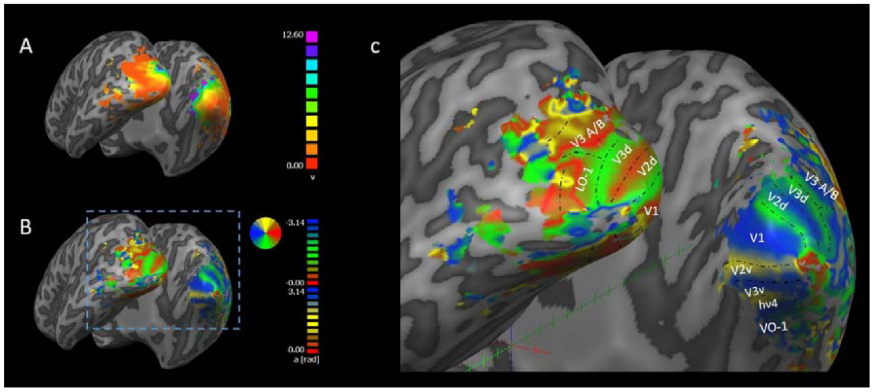

Figure 2. Visual field maps estimated for a subject. Eccentricity (a) and polar angle (b) maps, pooled from the pRF position parameters, were rendered on the inflated meshes and used to identify the boundaries of the visual areas (c). The colors represent the recording sites for which the pRF model explains at least 30% of the variance. Black lines and labels indicate the position of the visual areas identified in both hemispheres.

Statistical analysis

To study the relationship between pRF sizes, eccentricity, and optical properties, we reorganized the data into bins of 0.5º of eccentricity. Eccentricity-binned data were fitted by a simple linear regression as in Harvey & Dumoulin (2011). The normality of quantitative variables was assessed by Shapiro-Wilk tests and by graphical analysis. For comparison between groups, t-Student or Mann-Whitney U tests were used.

Results

The boundaries of area V1 were straightforwardly defined for all subjects. Based on visual inspection of the resulting visual field maps, there were no conspicuous irregularities in the retinotopic organization of subjects with intraocular lenses (IOLs)

Figure 3 shows the changes of the pRF sizes across visual field eccentricities within the primary visual cortex. As expected, pRF sizes increased with eccentricity.

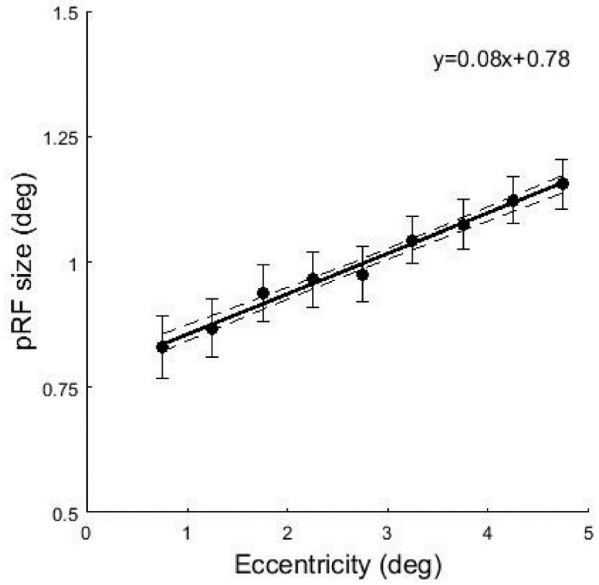

Figure 3. Changes in pRF size across visual field eccentricity in primary visual cortex. Error bars reflect the standard error of the mean (SEM) within each eccentricity bin. The solid lines represent the best-fitting functions described by the equation $y = \beta_1 x + \beta_0$, where y is the pRF size, x is the eccentricity and β_1 and β_0 are the slope and intercept, respectively. The dashed lines reflect 95% confidence intervals of these fits determined by bootstrapping the binned data and refitting.

Optical parameters and pRFs

To investigate the influence of optical parameters on cortical resolution, we divided the IOL group into sub-groups according to median optical parameters (table 1). Subjects´ total RMS, RMS_h, MTF at 10cpd, and Strehl ratio values equal or above the median were assigned to the group labeled as "**++**", while the remaining were assigned to the group "--." Changes in pRF size as a function of visual field eccentricity in the primary visual cortex of these sub-groups are shown in figure 4 and figures S1-S4 of the supplementary material. Our analysis revealed that subjects with worse optical resolution

have larger pRF sizes. In particular, significant differences were found between the mean pRF size of the sub-groups defined based on MTF_h (p=0.038).

Table 1 *Optical parameters obtained for patients implanted with multifocal IOLs at the 3rd post-operative week. The values were accessed using iTrace, which combines an aberrometer with corneal topography, for each eye and the mean was calculated for each participant.*

Optical parameters	Mean (SD)
RMS total	0.424 (0.129)
RMS_h	0.164 (0.051)
MTF h	0.313 (0.065)
MTF at 10 cpd	0.294 (0.101)
Strehl ratio	0.068 (0.034)

SD: standard deviation; RMS: Root mean square; RMS_h: RMS of higher order aberrations; MTF: modulation transfer function; MTF_h: MTF averaged height.

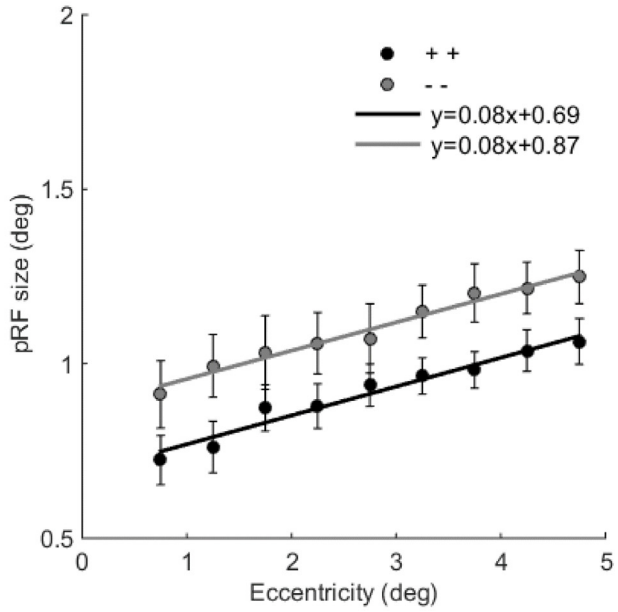

Figure 4. Comparison of the pRF sizes across visual field eccentricity between IOL sub-groups defined based on MTF_h. The black and grey colours represent the group of the subjects with MTF_h values above (or equal) and bellow the median, respectively. Error bars show the standard error of the mean (SEM) within each eccentricity bin and the solid lines show the best linear fit to bin means.

12

Relation between subjective quality of vision and pRFs

We evaluated the relation between subjective quality of vision and pRF measures (mean pRF size, β_0 and β_1). Using the total QoV questionnaire score and the "bothersome" (complaint) results, we divided subjects into two sub-groups (low and high score of complaints) based on the median value. We compared pRF measures between these sub-groups. Surprisingly, subjects with lower total scores (less complaints) had larger pRF sizes across visual field eccentricities (figure 5A). These differences between sub-groups were even more evident after taking into account the "bothersome" subscale (figure 5B). Moreover, β_0 and β_1 were significantly different between sub-groups (p=0.012 and p=0.020, respectively).

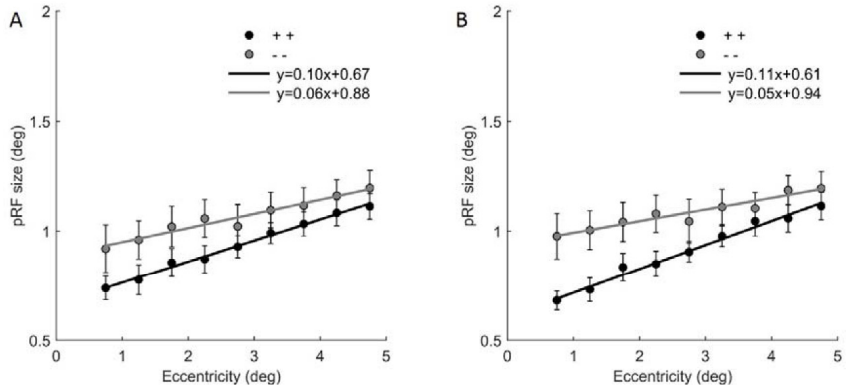

Figure 5. *Relation between subjective quality of vision and pRF sizes across primary visual cortex. (A) Comparison between subjects with higher and lower total quality of vision questionnaire score. (B) Comparison between the subjects feeling more and less bothered by dysphotic symptoms. Groups were defined based on the total score and "bothersome" results. The black colour represents the group with bothersome scoring higher or equal to the median (++) and grey colour represents the group with bothersome score lower than median (--). Error bars show the standard error of the mean (SEM) within each eccentricity bin and the solid lines show the best linear fit to bin means.*

Discussion

Our study demonstrated, for the first time, that optical properties of the eye influence pRF sizes and, consequently, cortical resolution of subjects who underwent recently bilateral sequential cataract surgery. Furthermore, our results showed a striking dissociation between optical parameters/pRFs and the perceived quality of vision, often even in opposing directions.

Through the application of novel stimuli for pRF modelling, we obtained efficient visual field maps similar to those achieved with more traditional stimuli.[9,31] Our pRF modelling results corroborate the commonly described pRF size pattern: pRF size increases as a function of eccentricity.[9,19,46]

There is a gap in the literature in trying to link quantifiable optical outcomes and quality of vision.[47] We suggest that studying properties of the visual cortex may be the first step to establish this association. Although it is generally accepted that the brain adapts to adverse/changed visual inputs, the mechanism behind this remains unknown.[48,49] Here, we took a step forward by evaluating the influence of optical parameters (total RMS, RMS_h, MTF at 10cpd, and Sthrel ratio) on cortical resolution of patients with multifocal IOLs. For this purpose, the IOL group was divided into two, based on the median value of the aforementioned optical properties. Our results showed that the sub-group with worse optical properties had larger pRF sizes in the striate cortex. Among all the optical properties that we studied, MTF seems to influence the most cortical processing. The sub-group of patients with lower values of average MTF height showed significantly higher mean pRF sizes in the primary visual cortex. The MTF translates the capacity of visual system to perceive the contrast of an image at a given spatial resolution and ranges from 0 to 1. In a perfect optical system, MTF is equal to 1, which indicates that maximum contrast was perceived. Therefore, we demonstrate that patients with lower image contrast also have a coarser cortical resolution.

Our visual perception is not merely determined by the analysis of an optically perfect image, but also by how the brain processes retinal input, as vision involves a "constructive" perception. Therefore, we evaluated subjective quality of vision through the validated QoV questionnaire.[28] Surprisingly, patients with more complaints, *i.e.* who felt more bothered by dysphotic symptoms at the 3rd week after cataract surgery, had significantly lower pRF size fitting interceptions and pRF size fitting slopes. This observation surprisingly dissociates subjective perception from cortical parameters.[50] In fact, some patients feel "unhappy" despite having excellent visual acuity measures after cataract surgery.[51] About 0.3-12% of these patients require IOL exchange, and even with the new diffractive trifocal intraocular lenses, the number of patients with severe symptoms remains high (about 6%).[52–56] It is well known that dysphotic phenomena such as glare, halos and starbursts (positive dysphotopsia) or even shadows, penumbra (negative dysphotopsia) are one of the main causes for patient's dissatisfaction.[52,53,57] Our results suggest that a more fine-tuned visual processing (with smaller pRF sizes) may allow more intense perception of dysphotic phenomena and therefore paradoxically worsened subjectively perceived quality of vision. Because these symptoms improve over time in some patients,[52,58] we hypothesize that there are other mechanisms involved in this adaptive process, possibly at a neuronal level, involving higher level brain regions. A longitudinal cohort study would allow evaluating whether there are alterations at the cortical processing level after cataract surgery in the long term.

In conclusion, this study highlights the potential use of pRF sizes as a quantitative measure of functional resolution of the visual cortex to objectively assess quality of vision. It shows the tight connection between optical properties and cortical resolution in patients with a recent change in their visual input, in the absence of fully established neuroadaptation, and helps to explain the often observed dissociation between optical parameters and subjectively perceived quality of vision.

Acknowledgments

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References

1. Kwongt KK, Belliveaut JW, Cheslert DA, et al. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. In: *Proceedings of the National Academy of Science of the United States of America*. Vol 89. ; 1992:5675-5679.
2. Bandettini PA, Wong EC, Hinks RS, Tikofsky RS, Hyde JS. Time course EPI of human brain function during task activation. *Magn Ressonance Med*. 1992;25(2):390-397. doi:10.1002/mrm.1910250220.
3. Ogawa S, Tank DW, Menon R, et al. Intrinsic signal changes accompanying sensory stimulation: Functional brain mapping with magnetic resonance imaging. *Proc Natl Acad Sci United States Am*. 1992;89:5951-5955.
4. Baseler HA, Brewer AA, Sharpe LT, Morland AB, Jägle H, Wandell BA. Reorganization of human cortical maps caused by inherited photoreceptor abnormalities Reorganization of human cortical maps caused by inherited photoreceptor abnormalities. *Nat Neurosci*. 2002;5(4). doi:10.1038/nn817.
5. Barnes GR, Hess RF, Dumoulin SO, Achtman RL, Pike GB. The cortical deficit in humans with strabismic amblyopia. *J Physiol*. 2001;533(1):281-297.

doi:10.1111/j.1469-7793.2001.0281b.x.

6. Victor JD, Apkarian P, Hirsch J, et al. Visual Function and Brain Organization in Non-decussating Retinal – Fugal Fibre Syndrome. *Cereb Cortex*. 2000;10(1):2-22. doi:10.1093/cercor/10.1.2.
7. D'Almeida OC, Mateus C, Reis A, Grazina MM, Castelo-branco M. NeuroImage Long term cortical plasticity in visual retinotopic areas in humans with silent retinal ganglion cell loss. *Neuroimage*. 2013;81:222-230. doi:10.1016/j.neuroimage.2013.05.032.
8. Baker CI, Peli E, Knouf N, Kanwisher NG. Reorganization of Visual Processing in Macular Degeneration. *J Neurosci*. 2005;25(3):614-618. doi:10.1523/JNEUROSCI.3476-04.2005.
9. Dumoulin SO, Wandell BA. Population receptive field estimates in human visual cortex. *Neuroimage*. 2008;39(2):647-660. doi:10.1016/j.neuroimage.2007.09.034.
10. Wandell BA, Dumoulin SO, Brewer AA. Visual Field Maps in Human Cortex. *Neuron*. 2007;56(2):366-383. doi:10.1016/j.neuron.2007.10.012.
11. Victor JD, Purpura K, Katz E, Mao B. Population encoding of spatial frequency, orientation, and color in macaque V1. *J Neurophysiol*. 1994;72(5):2154-2166.
12. Wandell BA, Winawer J. Computational neuroimaging and population receptive fields. *Trends Cogn Sci*. 2015;19(6):349-357. doi:10.1016/j.tics.2015.03.009.
13. Papanikolaou A, Keliris GA, Lee S, Logothetis NK, Smirnakis SM. NeuroImage Nonlinear population receptive fi eld changes in human area V5 / MT + of healthy subjects with simulated visual fi eld scotomas. *Neuroimage*. 2015;120:176-190. doi:10.1016/j.neuroimage.2015.06.085.
14. Schwarzkopf DS, Anderson EJ, Haas B De, White SJ, Rees G. Larger Extrastriate Population Receptive Fields in Autism Spectrum Disorders. *J Neurosci*. 2014;34(7):2713-2724. doi:10.1523/JNEUROSCI.4416-13.2014.
15. Brewer AA, Barton B. Effects of healthy aging on human primary visual cortex.

Health (Irvine Calif). 2012;4(I):695-702. doi:10.4236/health.2012.429109.

16. Levin N, Dumoulin SO, Winawer J, Dougherty RF, Wandell BA. Cortical maps and white matter tracts following long period of visual deprivation and retinal image restoration. *Neuron*. 2010;65(1):21-31. doi:10.1016/j.neuron.2009.12.006.Cortical.
17. Hoffmann MB, Kaule FR, Levin N, et al. Plasticity and stability of the visual system in human achiasma. *Neuron*. 2012;75(3):393-401. doi:10.1016/j.neuron.2012.05.026.Plasticity.
18. Song C, Samuel D, Kanai R, Rees G. Neural Population Tuning Links Visual Cortical Anatomy to Human Visual Perception. *Neuron*. 2015;85(3):641-656. doi:10.1016/j.neuron.2014.12.041.
19. Harvey BM, Dumoulin SO. The Relationship between Cortical Magnification Factor and Population Receptive Field Size in Human Visual Cortex: Constancies in Cortical Architecture. *J Neurosci*. 2011;31(38):13604-13612. doi:10.1523/JNEUROSCI.2572-11.2011.
20. Rodieck RW. Retinal organization. In: *The First Steps in Seeing*. 1st ed. Massachusetts: Sinauer Associates; 1998:194-208.
21. Smith AT, Singh KD, Williams AL, Greenlee MW. Estimating Receptive Field Size from fMRI Data in Human Striate and Extrastriate Visual Cortex. *Cereb Cortex*. 2001;11(12):1182-1190. doi:10.1093/cercor/11.12.1182.
22. Duncan RO, Boynton GM. Cortical Magnification within Human Primary Visual Cortex Correlates with Acuity Thresholds. *Neuron*. 2003;38(4):659-671. doi:10.1016/S0896-6273(03)00265-4.
23. Sabesan R, Yoon G. Visual performance after correcting higher order aberrations in keratoconic eyes. *J Vis*. 2009;9(5):1-10. doi:10.1167/9.5.6.Introduction.
24. Delahunt PB, Webster MA, Ma L, Werner JS. Long-term renormalization of chromatic mechanisms following cataract surgery. *Vis Neurosci*. 2004;21(3):301-307. doi:10.1017/S0952523804213025.

25. Campbell BYFW, Green DG. Optical and retinal factors affecting visual resolution. *J Physiol*. 1965;181(3):576-593. doi:10.1113/jphysiol.1965.sp007784.

26. Artal P, Chen L, Fernández EJ, Singer B, Manzanera S, Williams DR. Neural compensation for the eye ' s optical aberrations. *J Vis*. 2005;4(4):281-287. doi:10.1167/4.4.4.

27. Rosa A, Ângela M, Costa J, et al. Functional magnetic resonance imaging as an innovative tool to assess neuroadaptation after cataract surgery. In: *2016 ARVO Imaging in the Eye Conference*. SEATTLE; 2016.

28. Mcalinden C, Pesudovs K, Moore JE. The Development of an Instrument to Measure Quality of Vision : The Quality of Vision (QoV) Questionnaire. *Invest Ophthalmol Vis Sci*. 2010;51(11):5537-5545. doi:10.1167/iovs.10-5341.

29. Mcalinden C, Skiadaresi E, Moore J, Pesudovs K. Subscale Assessment of the NEI-RQL-42 Questionnaire with Rasch Analysis. *Invest Ophthalmol Vis Sci*. 2011;52(8):5685-5694. doi:10.1167/iovs.10-67951.

30. Brainard DH. The Psychophysics Toolbox. *Spat Vis*. 1997;10(4):433-436. doi:10.1163/156856897X00357.

31. Alvarez I, de Haas B, Clark CA, Rees G, Schwarzkopf DS. Comparing different stimulus configurations for population receptive field mapping in human fMRI. *Front Hum Neurosci*. 2015;9:1-16. doi:10.3389/fnhum.2015.00096.

32. Zuiderbaan W, Harvey BM, Dumoulin SO. Modeling center-surround configurations in population receptive fields using fMRI. *J Vis*. 2012;12(3):10-10. doi:10.1006/nimg.1998.0395.

33. Schira MM, Tyler CW, Breakspear M, Spehar B. The Foveal Confluence in Human Visual Cortex. *J Neurosci*. 2009;29(28):9050-9058. doi:10.1523/JNEUROSCI.1760-09.2009.

34. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. I. Segmentation and surface reconstruction. 1999;9(2):179-194. doi:10.1006/.

35. Parker DL, Gullberg GT. Signal to noise efficiency in magnetic resonance imaging.

Med Phys. 1990;17(2):250-257. doi:10.1118/1.596503.

36. Talairach J, Tournoux P. *Co-Planar Stereotaxic Atlas of the Human Brain. 3-Dimensional Proportional System: An Approach to Cerebral Imaging*. New York: Thieme; 1988.
37. Kriegeskorte N, Goebel R. An Efficient Algorithm for Topologically Correct Segmentation of the Cortical Sheet in Anatomical MR Volumes. *Neuroimage*. 2001;14(2):329-346. doi:10.1006/nimg.2001.0831.
38. Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis. II: inflation, flattening, and a surface-based coordinate system. 1999;9(2):195-207. doi:10.1006/nimg.1998.0396.
39. Wandell BA, Chial S, Backus BT. Visualization and measurement of the cortical surface. *J Cogn Neurosci*. 2000;12(5):739-572. doi:10.1162/089892900562561.
40. Senden M, Reithler J, Gijsen S, Goebel R. Evaluating Population Receptive Field Estimation Frameworks in Terms of Robustness and Reproducibility. *PLoS One*. 2014;9(12):1-30. doi:10.1371/journal.pone.0114054.
41. Sereno M, Dale A, Reppas J, et al. Borders of Multiple Visual Areas in Humans Revealed by Functional Magnetic Resonance Imaging. *Science (80-)*. 1995;268(5212):889-893. doi:10.1126/science.7754376.
42. Larsson J, Heeger DJ. NIH Public Access. *Off J Soc Neurosci*. 2006;26(51):13128-13142. doi:10.1523/JNEUROSCI.1657-06.2006.
43. Dougherty RF, Koch VM, Brewer AA, Modersitzki J, Wandell BA. Visual field representations and locations of visual areas V1 / 2 / 3 in human visual cortex. *J Vis*. 2003;3(10):586-598. doi:10.1167/3.10.1.
44. Larson AM, Loschky LC. The contributions of central versus peripheral vision to scene gist recognition. *J Vis*. 2009;9(10):1-16. doi:10.1167/9.10.6.Introduction.
45. Strasburger H, Jüttner M. Peripheral vision and pattern recognition : A review. *J Vis*. 2011;11(5):1-82. doi:10.1167/11.5.13.Contents.
46. Amano K, Wandell B a, Dumoulin SO. Visual field maps, population receptive field

sizes, and visual field coverage in the human MT+ complex. *J Neurophysiol*. 2009;102(5):2704-2718. doi:10.1152/jn.00102.2009.

47. Wilkins MR, Allan BD, Rubin GS, et al. Randomized Trial of Multifocal Intraocular Lenses versus Monovision after Bilateral Cataract Surgery. *Ophthalmology*. 2013;1290(12):2449-2456. doi:10.1016/j.ophtha.2013.07.048.
48. Rosa AM, Silva MF, Ferreira S, Murta J, Castelo-branco M. Plasticity in the Human Visual Cortex : An Ophthalmology-Based Perspective. 2013;2013:1-13.
49. Pepin S. Neuroadaptation of presbyopia-correcting intraocular lenses. *Curr Opin Ophthalmol*. 2008;19(1):10-12. doi:10.1097/ICU.0b013e3282f31758.
50. McAlinden C, Skiadaresi E, Gatinel D, Cabot F, Huang J, Pesudovs K. The Quality of Vision questionnaire: subscale interchangeability. *Optom Vis Sci*. 2013;90(8):760–764. doi:10.1097/OPX.0b013e3182993856.
51. Kinard K, Jarstad A, Olson RJ. Correlation of visual quality with satisfaction and function in a normal cohort of pseudophakic patients. *J Cart Refract Surg*. 2013;39(4):590-597. doi:10.1016/j.jcrs.2012.11.023.
52. de Vries NE, Webers CAB, Touwslager WRH, et al. Dissatisfaction after implantation of multifocal intraocular lenses. *J Cart Refract Surg*. 2011;37(5):859-865. doi:10.1016/j.jcrs.2010.11.032.
53. Woodward MA, Randleman JB, Stulting RD. Dissatisfaction after multifocal intraocular lens implantation. *J Cart Refract Surg*. 2009;35(6):992-997. doi:10.1016/j.jcrs.2009.01.031.
54. Calladine D, Jr E, Shah S, et al. Multifocal versus monofocal intraocular lenses after cataract extraction (Review) Multifocal versus monofocal intraocular lenses after cataract extraction. *Cochrane Database Syst Rev*. 2012;(9):3-5. doi:10.1002/14651858.CD003169.pub3.Copyright.
55. Dick HB, Dell S, Rosen E, Ali JL, Slade S. Efficacy and safety of multifocal intraocular lenses following cataract and refractive lens exchange : Metaanalysis of peer-reviewed publications. *J Cart Refract Surg*. 2016;42(2):310-328.

doi:10.1016/j.jcrs.2016.01.014.

56. Mendicute J, Kapp A, Pierre L, et al. Evaluation of visual outcomes and patient satisfaction after implantation of a diffractive trifocal intraocular lens. *J Cart Refract Surg*. 2016;42(2):203-210. doi:10.1016/j.jcrs.2015.11.037.

57. Holladay JT, Zhao H, Reisin CR. Negative dysphotopsia : The enigmatic penumbra. *J Cart Refract Surg*. 2012;38(7):1251-1265. doi:10.1016/j.jcrs.2012.01.032.

58. Bautista arlos P, Gonzalez DC, Gomez AC, Bescos JAC. Evolution of visual performance in 250 eyes implanted with the Tecnis ZM900 multifocal IOL. *Eur J Ophthalmol*. 2009;19(5):762-768.

Functional magnetic resonance imaging to assess neuroadaptation to multifocal intraocular lenses: a longitudinal study – original article number 5 (under review)

Functional magnetic resonance imaging to assess neuroadaptation to multifocal intraocular lenses: a longitudinal study

Running head: FMRI to assess neuroadaptation to multifocal lenses

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Abstract

Purpose

To investigate the use of functional magnetic resonance imaging (fMRI) to assess neuroadaptation to multifocal intraocular lenses (IOLs).

Setting

Faculty of Medicine, University of Coimbra, Portugal.

Design

Prospective fixed cohort study.

Methods

Thirty patients with bilateral diffractive IOL implantation following cataract surgery underwent functional MRI at post-operative intervals of 3 weeks and 6 months. A non-intervention control group (n=15) was included as proof of concept. Functional stimuli consisted in sinusoidal gratings with threshold contrast and a light source to induce disability glare. Subjective quality of vision and reading performance were assessed and wavefront analyses were conducted.

Results

Glare decreased the fMRI signal measured for sinusoidal gratings initially (3 weeks), but not at 6 months (p=0.04), as confirmed by contrast detection under glare improvement (p=0.002).

Patients showed increased activity of cortical areas involved in visual attention, procedural learning, effortful cognitive control and goal oriented behavior in the early post-operative period, which normalised at 6 months. There were no differences in aberrations, Strehl ratio or modulation transfer function, despite significant decreases of

questionnaire symptom scores, and visual acuity and reading performance improvement. The control group remained unchanged.

Conclusion

Neuroadaptation to multifocal IOLS takes place initially through recruitment of visual attentional and procedural learning networks. Thereafter, a form of long-term adaptation/functional plasticity occurs, leading to brain activity regularization towards a non-effort pattern. These findings are consistent with functional and questionnaire outcomes and are unrelated to optical properties, which reinforce the crucial role of higher-level brain regions in our perceptual construction of vision.

4

Introduction

Neuroadaptation is believed to represent an important factor determining favorable outcomes after multifocal intraocular lens (IOL) implantation, especially with regard to concerns of positive dysphotopsia (glare, haloes and starbursts).[1-3] Indeed, according to ASCRS/ESCRS survey updates on complications of foldable IOLs, the most common cause for explantation or secondary intervention after multifocal IOLs is the presence of disturbing glare/optical aberrations.[4] There is a lack of effective treatments for these complaints, leading in 4-12% of the cases to IOL explantation, which has remained a drawback to the more widespread use of multifocal IOLs.[1, 3, 5, 6]

Optical parameters *per se* are unable to explain these differences in outcomes, as higher-order aberrations, forward light scatter, pupil diameter and uncorrected visual acuity are similar in patients with and without dysphotic symptoms.[7, 8] There is no clear correlation between glare symptoms and optical quality parameters, even after excluding dry eye, posterior capsule opacification and retinal disease, that also cause decreased quality of vision.[7, 8]

Therefore, a more thorough understanding of neuroadaptive mechanisms could lead to better management of dysphotopsia and consequent improvement of multifocal IOL outcomes.

Neuroplasticity refers to the ability of the brain to reorganize its function and structure in response to changes in the environment.[9] Functional magnetic resonance imaging (fMRI) allows studying brain activity in vivo. It has been used to demonstrate the presence of neuroplasticity after refractive surgery, macular degeneration and in amblyopia.[10-12]

A recent study, published by our group, used fMRI to investigate the association between dysphotopsia and neural responses in visual and higher-level brain regions.[13] We found that patients recently implanted with multifocal IOLs had increased activity of cortical

areas dedicated to visual attention and effortful action (frontoparietal circuits), procedural learning, cognitive control (cingulate cortex) and to goal oriented behaviour (caudate).[13] Moreover, patients who were more bothered by visual symptoms showed even more increased activity in the top-down attentional network (parietal and frontal lobes) and had increased activity in the cingulate cortex and in the caudate nucleus. Such effects were not present in an age and gender-matched control group of healthy subjects and therefore likely represent the initial phase of neuroadaptation to multifocal lenses.[13]

Nonetheless, these findings should be endorsed in studies including a longer follow up, to allow comparison between early results and those obtained after neuroadaptation is fully implemented. We would expect to see a decrease in the activation of the aforementioned areas, as visual effort decreases, and an improvement of functional parameters.

Thus, in the present study we used functional magnetic resonance imaging to compare visual and higher-level cortical activity between the early post-operative period (3 weeks) and 6 months follow-up in patients implanted with multifocal IOLS.

Methods

Study design and participants

Observational, fixed cohort within-subject study of 30 patients with bilateral multifocal IOLs. Inclusion criteria: age < 75 years, absence of metallic foreign bodies, no surgical complications, pre-operative sphere in either eye less than 6 diopters (D) in magnitude, regular topography (sagittal maps displaying a relatively uniform color pattern centrally with a natural flattening in the periphery or symmetric "bow-tie" pattern along a single meridian with a straight axis on both sides of center), less than 1.5 D of corneal

astigmatism and no history of other ocular comorbidities, previous corneal or intraocular surgery and amblyopia. Non-toric multifocal lenses were implanted binocularly with approximately a 1-week interval, under topical anesthesia, through a 2.75 mm clear cornea incision in the steepest meridian. Patients received an Acrysof Restor SN6AD1 IOL (Alcon Surgical), an apodized hybrid lens, combining diffractive and refractive regions with a +3.00 addition.

As proof of concept, and to account for slight variations of measures due to confounding factors, a control group of 15 age and gender-matched subjects was included. These 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 less than 6 D in magnitude, regular topography and no history of comorbidities, metallic foreign bodies, previous corneal or intraocular surgery and amblyopia.

We excluded subjects with excessive head movement inside the magnetic scanner, with clinically significant cystoid macular edema or any late surgical complication.

Post-operative assessments were at 3 weeks (as soon as possible after surgery, at the same time allowing enough postoperative healing of the ocular structures) and at 6 months.

Researchers and technicians who performed the examinations and investigators who evaluated the fMRI images were blinded for the time point at which the images were acquired. Complete blinding was not possible because the control group required, at least, spectacles for near vision. Nevertheless, no automatic procedure related to neuroimaging, psychophysics, or aberrometry can be influenced by this type of unmasking.

Prior to participating, all subjects were provided with an information letter to be read at home, presenting the study as an effort to understand changes in the brain after cataract surgery.

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 participants were adequately informed and signed an informed consent form.

Ophthalmological examination

The ophthalmological examination consisted in 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, fundoscopy and tonometry. We used the Early Treatment Diabetic Retinopathy Study (ETDRS) charts for distance visual acuity and the Portuguese version of the Radner test (Radner-Coimbra Reading Charts) for measuring near visual acuity at 40 cm. [14] All measurements were taken under photopic conditions [80 candela (cd)/m^2].

Reading parameters were evaluated with the three Portuguese Radner-Coimbra Reading Charts. The charts were read binocularly in random order, at 40-cm. Patients uncovered and read sentence after sentence, as quickly and accurately as possible. Reading time was measured with a stopwatch. Reading speed in words per minute (wpm) was calculated based on the number of words in each sentence and the time needed to read it (14 words x 60 seconds divided by the reading time). The reading length limit was 20 seconds. Reading acuity was expressed in terms of logRAD, which is the reading equivalent of logMAR. The reading score was calculated as previously

reported[15] and allows comparing reading speed obtained under different conditions. Values closer to 100 reflect better reading speeds.

Optical properties

Total ocular and internal aberrations, Strehl ratio and modulation transfer function (MTF) were evaluated without spherico-cylindrical correction with the iTrace (version 6.0.1, Tracey Technologies), as previously described.[13] The best quality scan of the three manual wavefront scans measurements at 4 mm (after dilating the pupil) was selected for further analysis. The following data of the total ocular, internal and corneal optics were registered: the total root mean square (RMS), RMS of higher-order aberrations (HOAs) from 3rd- to 5th-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.

All parameters were selected with spherical-cylindrical correction in controls, to reflect clinical reality. The same rationale was applied for psychophysical assessment and fMRI, during which only patients with multifocal IOLs were not wearing spectacle correction.

Quality of Vision (QoV) questionnaire

The validated QoV questionnaire enables the measurement of subjective quality of vision on a 0-100 scales with higher scores indicating worse quality of vision. It consists of 10 questions with 3 subscales (frequency, severity, and bothersome) including glare, haloes, starbursts, hazy vision, blurred vision, distortion, double or multiple images, fluctuation in vision, focusing difficulties and depth perception difficulties.[16] The first seven symptoms have an associated picture to improve patient understanding. Participants rated their

perception of these symptoms at both visits and raw questionnaire data were Rasch-scaled to provide interval level measurement properties.

Optical coherence tomography (OCT) scan acquisition

Trained technicians acquired macular and optic nerve scans by using the Spectralis OCT (Heidelberg Engineering). These images were analyzed by one of the researchers to exclude retinal or optic nerve pathology.

Psychophysical assessment

Psychophysical assessment with the Method of Constant Stimuli in a forced-choice detection test determined the contrast threshold for each subject. The stimulus consisted of Gabor patches oriented at 90° with spatial phase of 180°, 2.5° of standard deviation size, spatial frequency of 10 cpd and mean luminance matching the background (20 cd/m^2).

Each participant completed two experimental runs with a surrounding luminance light source (simulating glare) of 13 cd/m^2 at 13° from the visual axis, and one without. A LED light tape was assembled on a square structure and a dimmer regulated its intensity. The light source induced disability glare, confirmed by significantly higher contrast detection thresholds when the lights were on (further details in Results). All components of the glare set up were non-magnetic and MRI compatible.

An experimental run consisted of 200 trials. Each trial comprised a stimulation phase where 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 and near threshold contrasts were obtained, for each run, taking the 50% and the 75% point, respectively.

Functional magnetic resonance imaging

FMRI studies are based on the blood oxygenation level dependent (BOLD) contrast that follows neuronal activity. When neurons become active the vascular system supplies more oxygenated haemoglobin than is needed by the neurons through an overcompensating increase in blood flow. This displaces the deoxygenated haemoglobin leading to a decrease in the deoxyhaemoglobin / oxyhaemoglobin ratio, which causes an increase in the MR signal of T2*–weighted images. Because the BOLD contrast mechanism uses oxyhaemoglobin and deoxyhaemoglobin as endogenous contrast agents, BOLD FMRI is non-invasive.

Participants performed two 3D anatomical magnetization prepared rapid-acquisition gradient echo (MPRAGE) and 7 functional runs: 3 retinotopic measurements (for detailed visual field mapping) in a block paradigm[17] and 4 contrast discrimination tasks, in an event related design, as previously reported.[13]

Functional task description

Contrast discrimination tasks were performed in the scanner using stimuli as in the psychophysical assessment, with (two runs) and without (two runs) a luminous source to induce disability glare. The same randomized sequences appeared in balanced pseudorandom luminance conditions (~50% of the participants started the task with the luminance source) to ensure that results were not influenced by eyestrain. Each run comprised four conditions resulting from three contrast levels, 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 x glare threshold. Each condition/event was repeated 16 times. The visual stimulus was present during 700ms, before a baseline fixation period. During this period, the subject answered if he/she saw the stimulus or not, by pressing one of two keys on a joystick (forced-choice paradigm), to maintain subject´s attention. The baseline fixation periods lasted 3300ms, 5300ms, or 7300ms, occurring randomly.

11

Although we repeated the psychophysical assessment in the second visit, we used the contrast levels obtained at the first visit for functional imaging in both visits, to be able to compare fMRI results between visits.

MRI data acquisition

We performed MRI acquisitions at the Brain Imaging Network facilities, on a 3-Tesla Magneton TIM Trio scanner (Siemens, Erlangen, Germany) equipped with a 32-Channel Head Coil (Siemens, Erlangen, Germany).

Functional images were acquired using a T2*-weighted GE echo-planar imaging (EPI) with TE=30 ms, TR=2000 ms, flip angle: 90°, 29 interleaved slices with voxel size 2 x 2 x2 mm, FOV 256 mm, for the block design paradigm; and TE=30 ms, TR=2000 ms, flip angle: 90°, 35 interleaved slices with voxel size 3 x 3 x3 mm, FOV 256 mm, for the event-related design paradigm. Visual stimuli were displayed on a LCD (Inroom Viewing Device, Nordic NeuroLab), positioned at the back of the scanner and viewed through a mirror attached to the head coil.

MRI data analysis

Anatomical and functional data processing and retinotopic mapping were performed using the Brain Voyager QX software (version 2.8.2, Brain Innovation B.V., Maastricht, The Netherlands).

Anatomical data processing

Three-dimensional T1-weighted anatomical images underwent brain extraction and intensity normalization. Two high-resolution anatomical MPRAGE were aligned to each other and averaged to improve the signal-to-noise ratio. The resulting anatomical images were then transformed to the Talairach coordinates. Afterwards, the cortex was automatically segmented and hand-edited to minimize segmentation errors. The cortical

surface was reconstructed at the white-gray matter border and rendered as a smooth 3D surface.

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 were also applied to the functional data acquired under the event-related design paradigm. Runs had to be excluded if head motion was more than one voxel (2/3mm for the block/event-related design, respectively), as head movement can result in artifacts, misalignment of the images and signal loss. Functional scans were aligned to each subject's structural scan in Tailarach space (a coordinate system of the human brain, normalized to map the location of brain structures independent from individual differences in the size and shape of the brain).

Statistical analysis

BOLD signal in the primary visual cortex

We ran a multi-study general linear model (GLM) for each subject separately to investigate the effect of the glare source in the early visual cortex. We applied a deconvolution analysis, which allows estimating the hemodynamic response function (HRF) for each event type (contrast condition).[18] The averaged BOLD responses were determined in the presence and absence of the glare source and for each selected region of interest (ROI) we obtained the mean condition effects (8 beta values).

Exploratory analysis of effort-related areas

A two-way analysis of variance (ANOVA) was conducted to compare each stimulation condition. We compared fMRI runs displaying a difficult visual stimulus (a glare threshold sinusoidal grating surrounded by a glare source) with fMRI runs displaying a more visible stimulus (a sinusoidal grating having 2.5 x the glare threshold) and no surrounding light source.

Using Rasch-scaled questionnaire scores, we divided patients into two groups (low and high-score) based on the median value of the bothersome score. We compared patients feeling more bothered by a visual symptom (high-score) 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 a random effects (RFX) group analysis with deconvolution design. The resulting group statistical maps were corrected for multiple comparisons using the false discovery rate (FDR) at p value < 0.05 or the Cluster-level Statistical Threshold Estimator (a plugin of the Brain Voyager software - which is used to analyze FMRI images - that provides a method for the correction of multiple comparisons, based on the number of contiguous voxels).

Sample size

The sample size was selected based on within-group comparisons, considering that in fMRI studies even small sample sizes (e.g. n = 10 per group) can achieve power of the order of 80-90% if the probabilities of activation are sufficiently separated (e.g. 15%–20% difference).[19] Because of the variability of the occurrence of dysphotopsia in patients implanted with multifocal IOLs, we decided to study a larger number of these subjects to represent as accurately as possible multifocal IOLs outcomes.

Quantitative data are described by median, 25th percentile and 75th percentile. The comparison of quantitative measures between the two visits was performed resorting to paired samples t-Student tests or Wilcoxon tests, according to whether normality

assumptions (assessed with Shapiro-Wilk tests) held. Correlations between each pair of normally distributed quantitative data were assessed by computing Pearson correlation coefficients. When at least one of the variables was not normally distributed, the Spearman correlation coefficient was computed instead. The analysis was performed on IBM SPSS Statistics 24 and on R 3.3.2. The level of significance adopted was 0.05.

Results

Demographics

In this prospective study we included 60 eyes of 30 patients (16 female) with ages ranging from 49 to 74 years (mean aged 61.03, standard deviation [SD] 6.08). An age and gender-matched (mean aged 61.07 years, SD 6.96, range 49-73) control group of 15 subjects (8 female) was also included.

We excluded four patients in the second visit due to cystoid macular edema (1 patient), excessive movement inside the scanner (2) and due to technical problems leading to rescheduling of the functional acquisition greater than two weeks (1). We excluded one subject in the control group due to excessive movement and another for the same technical problem mentioned above.

Glare impact on BOLD signal in the primary visual cortex

In the first study visit, the BOLD β max (peak value of the haemodynamic response curve BOLD signal after the stimulus is presented) and area under the curve (AUC) of response profiles to threshold stimuli in the primary visual cortex was significantly lower under glare than without glare in patients with multifocal IOLs (β max decreased from 0.10 (SEM – standard error mean ± 0.03) to 0.03 (SEM ± 0.04) and AUC decreased from 0.20 to 0.04,

without and with glare, respectively). P=0.04 and 0.05 for β2 and β3, respectively, Wilcoxon rank sum test.

At the second visit, however, the light source no longer decreased either BOLD β max or AUC in the primary visual cortex under the same experimental conditions (same level of contrast and light source intensity). β max without and with glare was 0.10 (SEM ± 0.041) and 0.113 (SEM ± 0.042), respectively; AUC was 0.158 and 0.170, without and with glare). Therefore, under the same conditions, patients were less affected by glare in the second visit, which is an objective measure of the improvement of disability glare at the visual cortical level, when subjects viewed threshold contrast stimuli (Fig 1).

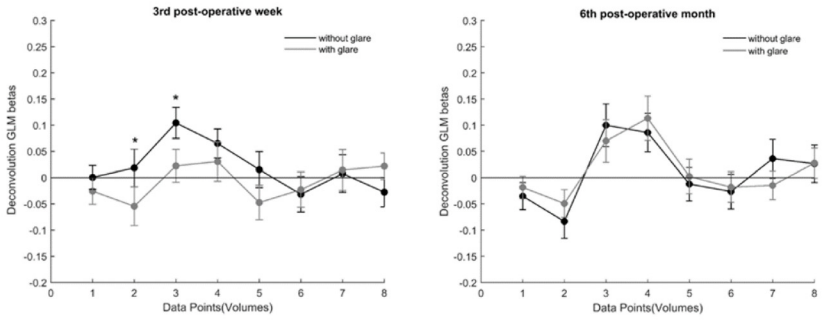


Figure 1. Average of estimated haemodynamic function response curves for glare threshold contrast within the primary visual cortex at the early post-operative period (left) and 6 months later (right). BOLD signal (beta values) are displayed as a function of time (each volume corresponding to 2 seconds). Following stimuli presentation, the BOLD signals peaks due to the compensatory increase in oxygenated hemoglobin (β max). Afterwards, it declines to a minimum before returning to baseline. Glare decreased BOLD signal in the primary visual cortex of recently operated patients, but not at the second visit (p> 0.05 for all data points at the second visit, Wilcoxon rank sum test) under the same experimental conditions.

16

This improvement was also supported by psychophysical data. Indeed, at the second visit patients were able to detect significantly lower contrast stimuli in the presence of glare. There was also a non-significant improvement of contrast detection thresholds in the absence of glare (Table 1).

	First visit (3 weeks)	Second visit (6 months)	P- value
NearThr_noglare	9.35 (6.93; 12.00)	7.77 (5.25; 13.37)	0.799
NearThr_glare	11.73 (6.89; 18.31)	9.54 (5.89; 13.89)	0.035
Thr_glare	9.63 (5.08; 12.88)	7.61 (4.45; 10.69)	0.002

Table 1. Contrast detection improvement over time in patients with multifocal IOLs. Data presented as median contrast percentage (25th percentile; 75th percentile). The p-values correspond to comparisons between the two visits and were computed with paired samples t-Student tests or Wilcoxon tests, as applicable. NearThr_noglare = near threshold contrast without glare; NearThr_glare = near threshold contrast under glare; Thr_glare = threshold contrast under glare.

Control subjects had no improvement in their contrast detection thresholds. The near threshold with glare was 3.84% (25th percentile 3.17, 75th percentile 5.27) and 4.54% (3.44, 4.83) in the first and second visits, respectively, p=0.433.

Attention network activation

At the first study visit, patients with multifocal IOLs had significant activation of the attention network, involving frontal, middle frontal, parietal frontal and the postcentral gyrus (multi-Subject RFX GLM, deconvolution analysis) when asked to discriminate a low-contrast stimulus under glare. There was also activation of the anterior cingulate gyrus (Fig 2). Six months later, however, there was only a relative activation of the middle frontal gyrus, under the same experimental conditions. The statistical maps were corrected using the Cluster-level Statistical Threshold Estimator plugin at $p<0.03$.

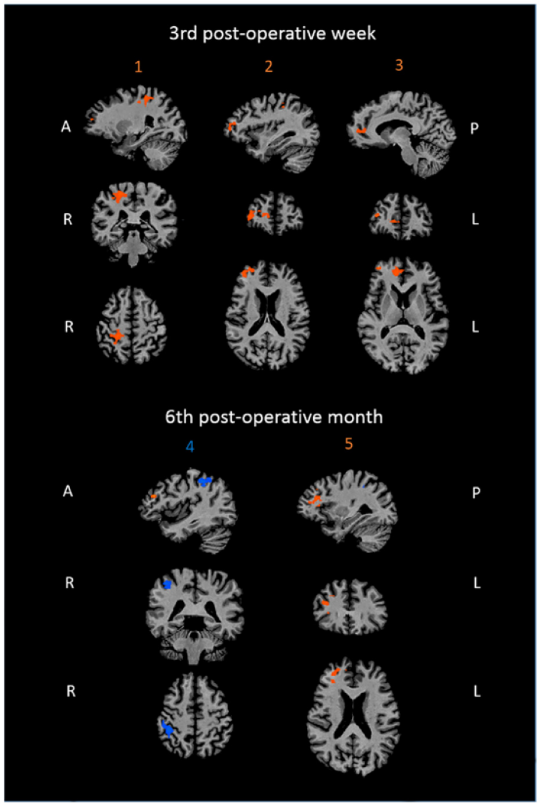


Figure 2. We performed a whole-brain analysis was at the first (upper image) and second visit, occurring 6 months later (bottom). A difficult stimulus (sinusoidal grating at contrast

threshold, under glare) was compared to a less difficult stimulus (having 2.5 x more contrast) without glare at both time points. In the first visit, there were activations in the parietal lobe (1), middle frontal gyrus (2) and cingulate gyrus (3). At the second visit, however, there is only a relative recruitment of the middle frontal gyrus (5).

Control subjects showed no significant effort, attention or learning cortical areas engagement in either the first or the second visits. They had relative occipital lobe and middle occipital gyrus deactivations when viewing the "difficult" stimulus, which is in accordance to the fact that the stimulus was less visible.

Quality of vision questionnaire and functional imaging results

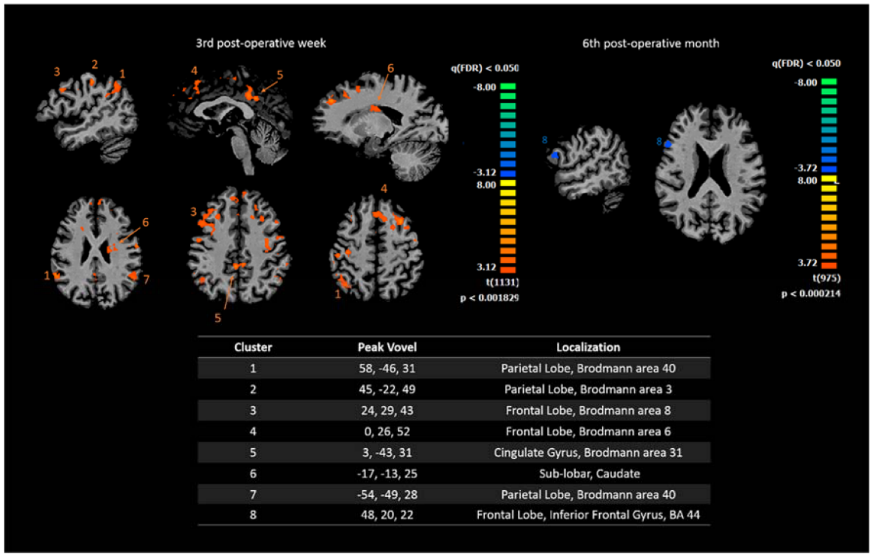
Quality of Vision scores assessing visual symptoms based on their frequency, severity, and bothersomeness for both study visits are presented in table 2. At the second visit, there was a statistically significant decrease in two questionnaire categories scores, indicating an improvement of patients' visual symptoms.

	First visit (3 weeks)	Second visit (6 months)	P- value
Frequency	43 (32; 61)	35 (15; 45)	0.063
Severity	37 (27; 47)	27 (13: 39)	0.003
Bothersomme	29 (14; 38)	7 (0; 34)	0.004

Table 2. Quality of Vision questionnaire scores of patients implanted with multifocal lenses. Higher scores indicate worse quality of vision. Data presented as median (25th percentile; 75th percentile). The p-values were computed with paired samples t-Student tests or Wilcoxon tests, as applicable.

We compared high-score patients (scoring higher than the median, therefore feeling more bothered by visual symptoms) with low-score patients, using the "bothersome" score obtained at the first study visit. Patients were asked to discriminate the same low-contrast stimulus (threshold) under glare in both study visits. At the first visit, the high-score group had significant activation of the frontal and parietal lobes, cingulate gyrus and caudate, q(FDR)< 0.05 (Fig 3). At the second visit, however, there were no significant differences in fMRI activations between groups. Because the high-score group bothersome score decreased from 46.0 to 29.2 and the low-score group from 16.9 to 7.8, it becomes clear that there was a significant improvement in quality of vision symptoms 6 months after surgery, in accordance to the fMRI findings.

The control group had no significant changes between visits, having a median "bothersome" score of 14 (0; 29, 25th and 75th percentiles, respectively) at the first visit and 23 (0; 29) at the second visit, p=0.138, Wilcoxon tests.



Cluster	Peak Vovel	Localization
1	58, -46, 31	Parietal Lobe, Brodmann area 40
2	45, -22, 49	Parietal Lobe, Brodmann area 3
3	24, 29, 43	Frontal Lobe, Brodmann area 8
4	0, 26, 52	Frontal Lobe, Brodmann area 6
5	3, -43, 31	Cingulate Gyrus, Brodmann area 31
6	-17, -13, 25	Sub-lobar, Caudate
7	-54, -49, 28	Parietal Lobe, Brodmann area 40
8	48, 20, 22	Frontal Lobe, Inferior Frontal Gyrus, BA 44

Figure 3. Patients feeling more bothered by dysphotic symptoms at the first visit were compared to those less bothered when both had to discriminate a low-contrast stimulus under glare. The high-score group (more bothered) showed significantly increased activity in several regions in the frontal and parietal lobes, as well as cingulate gyrus and caudate activations (q (FDR) <0.05) at the first visit, but not 6 months later.

Visual acuity and reading performance

Monocular distance refraction showed a median spherical error of 0.0D (25th percentile -0.5D; 75th percentile 0.06) in right eyes and 0.0D (-0.25; 0.25) in left eyes at the first visit. At the second visit, the median spherical error was 0.0D (-0.25; 0.25) both in right and left eyes. Median refractive astigmatism was -0.50D (-0.56; -0.19) and -0.50D (-0.75; 0) in right and left eyes, respectively at the first visit and -0.50D (-0.56; -0.19) and -0.25D (-0.75; 0.0) in right and left eyes, respectively, at the second visit.

One patient developed posterior capsule opacification requiring Nd:YAG laser capsulotomy.

Distance and near visual acuities improved at 6 months in patients implanted with multifocal IOLs (table 3).

	First visit	Second visit	P- value
UDVA (logMAR)	0.05 (0.00; 0.14)	-0.03 (-0.08; 0.08)	0.016
CDVA (logMAR)	-0.02 (-0.06; 0.04)	-0.08 (-0.14; -0.06)	<0.001
UNVA (logRAD)	0.20 (0.10; 0.20)	0.10 (0.10; 0.20)	0.002
CNVA (logRAD)	0.10 (0.10; 0.20)	0.10 (0.00; 0.10)	0.001

Table 3. Binocular visual acuities of patients implanted with multifocal lenses at post-operative intervals of 3 weeks and 6 months. Data presented as median (25th percentile; 75th percentile). The p-values were computed with paired samples t-Student tests or Wilcoxon tests, as applicable. UDVA = uncorrected distance visual acuity; CDVA = corrected distance visual acuity; UNVA = uncorrected near visual acuity; CNVA = corrected near visual acuity.

There was also a statistically significant improvement in reading performance at 6 months, including reading speed, reading acuity, maximum reading speed and reading score, as evaluated with the Radner-Coimbra Reading Charts (table 4).

	First visit	Second visit	p- value
Reading speed (wpm)	126.94 (113.36; 159.97)	140.33 (120.72; 181.39)	0.025
Reading acuity (logRAD)	0.20 (0.10; 0.21)	0.10 (0.01; 0.20)	0.007
Max reading speed (wpm)	195.40 (171.08; 226.42)	218.75 (191.34; 240.00)	0.006
Reading score	87.57 (85.71; 90.55)	88.98 (86.78; 91.82)	0.006

Table 4. Reading performance improved significantly in patients implanted with multifocal IOLs 6 months after surgery, in comparison with the 3rd week visit. Data presented as median (25th percentile; 75th percentile). The p-values were computed with paired samples t-Student tests or Wilcoxon tests, as applicable. Wpm = words per minute; logRAD = logarithm of the reading acuity determination.

There were no significant changes in either visual acuities or reading performance parameters in control subjects between the first and second study visits.

Optical properties

Patients had no improvement in optical properties at the second study visit (table 5). There was no correlation between the optical properties that we measured (total RMS, higher-order RMS, average MTF height, MTF for 10 cpd spatial frequency, Strehl ratio) and questionnaire scores (either frequency, severity or bothersome) in both visits, Pearson or Spearman correlations, $p>0.05$.

In both study visits, patients' contrast detection thresholds were weak to moderate, 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 at the first study visit. At the second visit, correlation coefficients were r=-0.56 and r=-0.49 and P values 0.01 and 0.02 for average MTF and MTF at 10 cpd, respectively. Contrast detection thresholds were positively correlated with total RMS, with Spearman coefficients of $\rho=0.62$, P=0.001 and $\rho=0.65$, P=0.001 at the first and second visits, respectively.

The control group had similar wavefront data in the first and second visits.

	First visit	Second visit	p- value
Total RMS (μm)	0.38 (0.31; 0.53)	0.40 (0.32; 0.52)	0.614
Higher-order RMS (μm)	0.14 (0.11; 0.19)	0.15 (0.10; 0.18)	0.204
Average MTF height	0.32 (0.23; 0.35)	0.30 (0.27; 0.38)	0.826

MTF for 10 cpd spatial frequencies	0.28 (0.19; 0.35)	0.25 (0.22; 0.40)	0.712
Strehl ratio	0.05 (0.03; 0.08)	0.05 (0.05; 0.10)	0.455

Table 5. Wavefront analysis of patients implanted with multifocal IOLs at the early post-operative period and 6 months later. Data presented as median (25th percentile; 75th percentile). The p-values were computed with paired samples t-Student tests or Wilcoxon tests, as applicable. All wavefront data was obtained from right eyes without spectacle correction. Left eye values were similar. Total RMS = Total eye root mean square; MTF = modulation transfer function.

Discussion

Despite the apparent importance of neuradaptation to multifocal IOL outcomes[1], the phenomena has remained poorly understood and, to the best of our knowledge, no studies have demonstrated its occurrence in the human brain. It is a phenomenon one would hope it would occur, especially to the most dissatisfied patients, after achieving a perfect refractive result, addressing dry eye, ruling out posterior capsule opacification and macular pathology.

Previous studies have found no correlation between optical parameters and multifocal IOL outcomes, as forward light scatter, higher-order aberrations, pupil diameter and uncorrected visual acuity are similar in patients with and without dysphotic symptoms.[7, 8]

In the present study, we used fMRI to evaluate neuroadaptation in patients implanted with bilateral multifocal lenses at two post-operative time points, 3 weeks and 6 months. This period was chosen according to clinical experience and literature consultation, as a reasonable time interval for improvements to occur[20] and to avoid potential carry-over

effects that could be present if the fMRI experiments were repeated sooner. We analysed the impact of a glare source on the visual cortex and on higher-level areas, i.e. effort related regions of the human brain.

We found out that glare significantly decreases visual cortex activation to a threshold stimulus in the early post-operative period, but that this effect is no longer present 6 months later, meaning that patients are eventually more able to discriminate low contrast stimuli, despite the presence of glare. This is an objective measure of the improvement of disability glare, at the cortical level. Indeed, previous studies have shown a fMRI response enhancement in the visual cortex associated with the development of expertise in visual tasks, and reduction of effective effort for a preserved level of task efficacy.[21]

We used threshold contrast stimuli to impose detection of subtle changes and to reflect common vision conditions, as contrast sensitivity is an assay of basic spatial vision. Stimuli had intermediate/high spatial frequencies (10 cpd) because these have a dominant ecological role in representation of the world.[22]

The light source intensity and position were set to induce only disability glare (loss of retinal image contrast as a result of intraocular light scatter) although avoiding dazzling and discomfort glare, which trigger nociceptive cortical circuits outside the scope of this study. Disability glare was validated at the psychophysics laboratory, before being transferred to functional magnetic imaging.

At the second visit (6 months), psychophysical assessment showed a statistically significant decrease in contrast detection thresholds in the presence of glare, which confirms that patients are able to detect lower contrast targets at this visit. As expected, at both study visits, contrast detection thresholds were negatively correlated with average MTF and MTF at 10 cpd and were positively correlated with total RMS, indicating that patients with more aberrations had a higher contrast detection threshold. As other

authors have reported before, there was also no correlation between the optical properties we measured and questionnaire scores in the present study.

In a recent study, we performed fMRI whole brain analyses to find out which cortical areas are recruited specifically in operated patients.[13] When asked to discriminate low-contrast stimuli under glare (difficult stimuli) in comparison with higher contrast stimuli without glare, patients showed significant activations of the attention network (frontal, middle frontal, parietal frontal and the postcentral gyrus), confirming that top-down attentional and effort-related networks had to be activated to discriminate threshold stimuli.[13]

In the present study, we compared these results with the 6th month data. At the second visit, there was only a relative recruitment of the middle frontal gyrus, meaning that less effort-related areas had to be activated for stimuli discrimination. Indeed, it has been shown that cortical regions associated with the attentional network are less activated after learning a visual task, and the decrease in brain activation is highly correlated with the magnitude of expertise acquisition and performance improvement.[23] Although there was no visual task training in our experiment, as the visual task was repeated only once at the 6th month follow-up, we can consider every day vision after surgery as a learning experience. Patients are exposed to glare sources and low contrast stimuli on a daily basis, and repeated experience with a visual stimulus can result in improved perception of the stimulus, i.e., perceptual learning.[23] Perceptual learning refers to experience-induced changes in the way perceivers pick up information.[24] With practice, humans become attuned to the relevant features and, over time, come to extract these with increasing selectivity and fluency.[24] The reduction of activation in attention-related areas during learning may represent a reduced requirement for attention as the task becomes easier due to improved processing efficacy.[21, 23]

Furthermore, we wanted to know if this cortical regularization of activity towards a non-effort pattern was also present in those patients with more pronounced visual symptoms at the first study visit (3 weeks). Therefore, we divided patients into two groups based on the "bothersome score" of the quality of vision questionnaire. Patients who were more bothered by visual symptoms had more activity in the top-down attentional network, in the cingulate cortex and in the caudate nucleus in the first visit. At the second visit (6 months), however, there were no significant differences in fMRI activations between groups, in accordance with the improvements in symptoms (figure 3 and table 2). Again, this likely reflects that patients more bothered by dysphotic symptoms required increased activity of the attentional network at the first visit, which facilitates perceptual learning through an interaction of attention-related and visual cortical regions.[23]

This interpretation is consistent with previous reports on perceptual learning. Early in training, subjects detect the target in a visual task only by paying close attention, whereas, after learning, the development of a target template in the visual cortex allows for effortless and more automatic discrimination, requiring less on-line top-down control.[21] The resultant effect of plasticity is, therefore, a progressive optimisation of neuronal responses elicited by the task and a minimization of the departure from the default state, due to increased processing efficacy.[25]

The cingulate gyrus region has an important role in attention, goal-directed behaviours and error monitoring, which explains its relative activation in the first study visit, when neuroadaptation has just started taking place, but no longer at the second visit, when task performance efficacy is improved.[26] The same rationale applies to the relative absence of caudate activations in the second visit, as this sub-cortical region is involved in the planning and execution of strategies to attain complex/difficult goals.[27] Indeed, increasing the difficulty of a problem to be solved results in increased activity in the caudate nucleus.[28] Conversely, if the task is no longer difficult and completed in a more

automatic way (no longer goal-oriented) there is no relative increased activation in this region.

These results are also supported by the aforementioned psychophysical outcomes (improvement in contrast detection under glare at 6 months) and by questionnaire scores. Indeed, there was an improvement in the QoV questionnaire scores in patients at the second visit, reaching statistical significance in the severity and bothersome subscales. In addition, there was a statistically significant improvement in visual acuity and in reading performance (reading speed, reading acuity, maximum reading speed and reading score, table 4) in patients at the 6th month follow-up.

Because these results could be attributed to an improvement in optical properties, we performed wavefront analysis with a ray-tracing aberrometer at both study visits. Ray-tracing has been shown to yield relatively accurate measurements of spherical aberration in the presence of multifocal IOLs.[29] There were no significant changes between visits in total RMS, higher-order RMS, average MTF height, MTF for 10 cpd spatial frequencies and Strehl ratio (table 5). This fact highlights that the improvements noted in our study were likely to be unrelated to the optical properties evaluated.

To account for time-dependent changes and task learning effects, we also studied a control group of healthy subjects, age- and gender-matched. As expected, the control group remained stable throughout the study, with no significant changes in any of the aforementioned tests.

Considering that the purpose of this study was to identify neuroadaptation to a recently implanted IOL, it was important to have a healthy control group completely adapted to a stable optical system. Additionally, because dysphotpsia and neuroadaptation may also occur with monofocal lenses, particularly in the early post-operative period, the control group included only subjects without previous intraocular surgery. This allowed

testing the critical difference between a clinical group undergoing adaptation and a control group not undergoing adaptation.

Therefore, our results may be applicable to all IOL adaptations and may not be specific to multifocal IOLs. It would also be interesting, in the future, to compare adaptation in patients undergoing cataract surgery with monofocal versus multifocal IOL implantation. In addition, it would be clinically relevant to study neuroadaptation to different IOLs designs and functional connectivity among visual and attention-related areas, especially in patients in which adaptation failed to occur. Specifically, corticostriatal loops contribute to the interpretation of ambiguous visual scenes, which may be the case in the presence of haloes, glare and starbursts.[30] Furthermore, successful learners in visual categorization learning are more likely to initially recruit the caudate than less successful ones.[30]

Therefore, understanding neuroadaptation at the cortical level will help bridging the gap between optical properties and subjective symptoms, leading to improved prevention and treatment of dysphotopsia.

In conclusion, this study shows, for the first time, that neuroadaptation to multifocal IOLs occurs through a process of attentional network, sub-cortical caudate and cingulate recruitment in the initial post-operative period. A form of long-term adaptation/functional plasticity occurs (probably perceptual learning) leading to a regularization of brain activity towards a non-effort neural activation pattern. It is likely that this change in activity represents an increase in neural efficiency such that fewer brain regions are required to perform the tasks, as previously found for gaining of expertise in computer game tasks. The fMRI findings we present are supported by functional results (visual acuity, reading performance, contrast detection), by questionnaire scores and are unrelated to optical properties, which reinforce the crucial role of the brain in our perceptual construction of vision.

What was known

Dysphotopsia are important causes of dissatisfaction after cataract surgery with mulifocal IOLs implantation.

Dysphotopsia tend to improve over time and it is believed that neuroadaptation plays an important role in this improvement, but the phenomenon remains poorly understood.

What this paper adds

There is recruitment of visual attentional and procedural learning networks of the human brain in the initial postoperative period.

Long-term adaptation/ functional plasticity leads to brain activity regularization towards a non-effort pattern at 6 months.

There is accompanying improvement of symptoms, visual acuity and contrast detection, independently of optical factors.

References

1 Rosen E, Alio JL, Dick HB, Dell S, Slade S. Efficacy and Safety of Multifocal Intraocular Lenses Following Cataract and Refractive Lens Exchange: Metaanalysis of Peer-Reviewed Publications. J Cataract Refract Surg 2016; 42: 310-328

2 Braga-Mele R, Chang D, Dewey S, Foster G, Henderson BA, Hill W, Hoffman R, Little B, Mamalis N, Oetting T, Serafano D, Talley-Rostov A, Vasavada A, Yoo S, Committee ACC. Multifocal Intraocular Lenses: Relative Indications and Contraindications for Implantation. J Cataract Refract Surg 2014; 40: 313-322

3 de Vries NE, Webers CA, Touwslager WR, Bauer NJ, de Brabander J, Berendschot TT, Nuijts RM. Dissatisfaction after Implantation of Multifocal Intraocular Lenses. J Cataract Refract Surg 2011; 37: 859-865

4 Mamalis N, Brubaker J, Davis D, Espandar L, Werner L. Complications of Foldable Intraocular Lenses Requiring Explantation or Secondary Intervention--2007 Survey Update. J Cataract Refract Surg 2008; 34: 1584-1591

5 Woodward MA, Randleman JB, Stulting RD. Dissatisfaction after Multifocal Intraocular Lens Implantation. J Cataract Refract Surg 2009; 35: 992-997

6 Calladine D, Evans JR, Shah S, Leyland M. Multifocal Versus Monofocal Intraocular Lenses after Cataract Extraction. Cochrane Database Syst Rev 2012: CD003169

7 Wilkins MR, Allan BD, Rubin GS, Findl O, Hollick EJ, Bunce C, Xing W, Moorfields IOLSG. Randomized Trial of Multifocal Intraocular Lenses Versus Monovision after Bilateral Cataract Surgery. Ophthalmology 2013; 120: 2449-2455 e2441

8 Kinard K, Jarstad A, Olson RJ. Correlation of Visual Quality with Satisfaction and Function in a Normal Cohort of Pseudophakic Patients. J Cataract Refract Surg 2013; 39: 590-597

9 Nelson CA. Neural Plasticity and Human Development: The Role of Early Experience in Sculpting Memory Systems. Developmental Science 2000; 3: 115-130

10 Martins Rosa A, Silva MF, Ferreira S, Murta J, Castelo-Branco M. Plasticity in the Human Visual Cortex: An Ophthalmology-Based Perspective. Biomed Res Int 2013; 2013: 568354

11 Vuori E, Vanni S, Henriksson L, Tervo TM, Holopainen JM. Refractive Surgery in Anisometropic Adult Patients Induce Plastic Changes in Primary Visual Cortex. Acta Ophthalmol 2012; 90: 669-676

12 Dilks DD, Baker CI, Peli E, Kanwisher N. Reorganization of Visual Processing in Macular Degeneration Is Not Specific to the "Preferred Retinal Locus". J Neurosci 2009; 29: 2768-2773

13 Rosa AM, Miranda ÂC, Patrício M, McAlinden C, Silva FL, Murta JN, Castelo-Branco M. Functional Magnetic Resonance Imaging to Assess the Neurobehavioral Impact of Dysphotopsia with Multifocal Intraocular Lenses. Ophthalmology

14 Rosa AM, Farinha CL, Radner W, Diendorfer G, Loureiro MF, Murta JN. Development of the Portuguese Version of a Standardized Reading Test: The Radner-Coimbra Charts. Arq Bras Oftalmol 2016; 79: 238-242

15 Radner W, Radner S, Raunig V, Diendorfer G. Reading Performance of Monofocal Pseudophakic Patients with and without Glasses under Normal and Dim Light Conditions. J Cataract Refract Surg 2014; 40: 369-375

16 McAlinden C, Pesudovs K, Moore JE. The Development of an Instrument to Measure Quality of Vision: The Quality of Vision (Qov) Questionnaire. Invest Ophthalmol Vis Sci 2010; 51: 5537-5545

17 Dumoulin SO, Wandell BA. Population Receptive Field Estimates in Human Visual Cortex. Neuroimage 2008; 39: 647-660

18 Serences JT. A Comparison of Methods for Characterizing the Event-Related Bold Timeseries in Rapid Fmri. Neuroimage 2004; 21: 1690-1700

19 Bhaumik DK, Roy A, Lazar NA, Kapur K, Aryal S, Sweeney JA, Patterson D, Gibbons RD. Hypothesis Testing, Power and Sample Size Determination for between Group Comparisons in Fmri Experiments. Stat Methodol 2009; 6: 133-146

20 Rabsilber TM, Rudalevicius P, Jasinskas V, Holzer MP, Auffarth GU. Influence of +3.00 D and +4.00 D near Addition on Functional Outcomes of a Refractive Multifocal Intraocular Lens Model. J Cataract Refract Surg 2013; 39: 350-357

21 Lewis CM, Baldassarre A, Committeri G, Romani GL, Corbetta M. Learning Sculpts the Spontaneous Activity of the Resting Human Brain. Proc Natl Acad Sci U S A 2009; 106: 17558-17563

22 Fiorentini A, Maffei L, Sandini G. The Role of High Spatial Frequencies in Face Perception. Perception 2013; 42: 1151-1157

23 Mukai I, Kim D, Fukunaga M, Japee S, Marrett S, Ungerleider LG. Activations in Visual and Attention-Related Areas Predict and Correlate with the Degree of Perceptual Learning. J Neurosci 2007; 27: 11401-11411

24 Kellman PJ, Garrigan P. Perceptual Learning and Human Expertise. Phys Life Rev 2009; 6: 53-84

25 Sigman M, Pan H, Yang Y, Stern E, Silbersweig D, Gilbert CD. Top-Down Reorganization of Activity in the Visual Pathway after Learning a Shape Identification Task. Neuron 2005; 46: 823-835

26 Choi MH, Kim HS, Yoon HJ, Lee JC, Baek JH, Choi JS, Tack GR, Min BC, Lim DW, Chung SC. Increase in Brain Activation Due to Sub-Tasks During Driving: Fmri Study Using New Mr-Compatible Driving Simulator. J Physiol Anthropol 2017; 36: 11

27 Grahn JA, Parkinson JA, Owen AM. The Cognitive Functions of the Caudate Nucleus. Prog Neurobiol 2008; 86: 141-155

28 Dagher A, Owen AM, Boecker H, Brooks DJ. Mapping the Network for Planning: A Correlational Pet Activation Study with the Tower of London Task. Brain 1999; 122 (Pt 10): 1973-1987

29 Jun I, Choi YJ, Kim EK, Seo KY, Kim TI. Internal Spherical Aberration by Ray Tracing-Type Aberrometry in Multifocal Pseudophakic Eyes. Eye (Lond) 2012; 26: 1243-1248

30 Lopez-Paniagua D, Seger CA. Interactions within and between Corticostriatal Loops During Component Processes of Category Learning. J Cogn Neurosci 2011; 23: 3068-3083

PART III

DISCUSSION AND FUTURE PERSPECTIVES

Neuroadaptation/neuroplasticity in the setting of multifocal intraocular lenses (IOLs) remains an outstanding clinical research question. The focus of attention has been so far in quantifying optical parameters, such as light scatter and intraocular aberrations. However, it has become clear that attempts to link quantifiable optical outcomes and dysphotopsia have not succeeded in proving a clear association between measurable aberrations and symptoms.[37] Another approach to evaluate the improvement over time has been the use of questionnaires. Quality of vision is a subjective entity based on an individual's perception of his or her vision. This perception is multifactorial, consisting not only of visual factors but also of psychological factors. Therefore, it is always difficult to evaluate a lens or a surgical outcome, even in the long term, based on the subjective result of a questionnaire. Although the previous approaches were undoubtedly very important, this thesis provides an integrative analysis of cortical activity, psychophysical performance and effort assessment. With functional magnetic resonance imaging (FMRI) it was possible to discover the interplay of these aspects of vision.

FMRI studies are based on the blood oxygenation level dependent (BOLD) contrast that follows neuronal activity. When neurons become active the vascular system supplies more oxygenated haemoglobin than is needed by the neurons through an overcompensating increase in blood flow.[38] This displaces the deoxygenated haemoglobin leading to a decrease in the deoxyhaemoglobin / oxyhaemoglobin ratio. Considering that oxyhaemoglobin is diamagnetic and deoxyhaemoglobin paramagnetic, a decrease in deoxyhaemoglobin/ oxyhaemoglobin ratio causes an increase in the MR signal of T2–weighted images.[39] Because the BOLD contrast mechanism uses oxyhaemoglobin and deoxyhaemoglobin as endogenous contrast agents, BOLD FMRI is non-invasive.[38, 40]

When a stimulus is visible, it will elicit an increase in the visual cortex BOLD signal. Human imaging shows increasing activity in the primary visual cortex with increases in stimulus contrast.[41] Threshold stimuli, by definition, are just visible and therefore elicit a weak signal. The threshold parameter reflects the transition from non-detectability as conceptualized by the psychometric function relating the probability of correct detection to the stimulus intensity.[42]

We chose to use contrast discrimination tasks to test neuroadaptation because contrast sensitivity is an assay of basic spatial vision and its improvement has been objectively demonstrated with time after multifocal IOL implantation.[43]

Clinical experience has shown that patients have more difficulties in visual tasks involving artificial lights in low light conditions, such as night driving. Evaluating cortical contrast responses under a glare source therefore was a suitable strategy to replicate these "real world" conditions. Given that subjective symptoms are related to glare, we expected that neuroadaptation would be maximized by exposure to glare stimuli, which was confirmed by our results.

We evaluated patients implanted with multifocal intra-ocular lenses at the early post-operative period (3 weeks) and at the 6th month. Patients underwent ophthalmological examination, psychophysical assessment for contrast thresholds determination (with and without glare), reading performance evaluation, topography and wavefront measurements, quality of vision questionnaire and functional magnetic resonance imaging. Although it would be interesting to perform the FMRI also before cataract surgery, this approach is hindered by the fact that cataract is not a uniform disease and that visual complaints and ability to perform the FMRI tasks would depend on the subtype of cataract. We evaluated patients implanted with the Acrysof Restor SN6AD1 IOL, an apodized hybrid IOL combining diffractive and refractive regions with a +3.00 D add. This IOL has a symmetric biconvex design with negative spherical aberration and a blue light–filtering chromophore.[44] It is one of the most widely used lens designs and therefore it provided an interesting perspective for clinical application.

Our group also developed the Portuguese version of the Radner test (Radner-Coimbra Charts) because routine single optotype distance visual acuity tests have been shown to be poor predictors for reading performance.[45, 46] In modern society, the ability to read is essential for daily life. The loss of this ability has a severe impact on quality of life, with loss of independence and productivity.[47, 48] Modern reading charts, as the highly standardized Radner Reading Charts, allow the simultaneous evaluation of reading acuity and reading speed.[48] They provide increased accuracy for the evaluation of near visual performance, which has become a valuable clinical tool as a pre and postoperative measure and for visual rehabilitation.[48] They consist in standardized highly comparable sentences in terms of lexical difficulty, syntactical complexity, word length, number of syllables and position of words.

We used the Quality of Vision (QoV) questionnaire because it is a 2nd generation questionnaire, unlike most dysphotopsia questionnaires, which are first generation.[49] First generation questionnaires assume that the space between response categories is equidistant and that all questions have the same value. They cannot be used in statistical analysis of correlation or change. Rasch analysis solves this problem and was used for scoring the QoV questionnaire answers. The QoV evaluates 10 symptoms (glare, halos, starbursts, hazy vision, blurred vision, distortion, double or multiple images, fluctuations, focusing difficulties and difficulty judging depth) with pictures to elucidate each term meaning. Each symptom has three questions associated with it about the frequency, severity and bothersome of the symptom.

The FMRI experiment involved retinotopy for visual cortex mapping and the aforementioned functional task, in which subjects had to discriminate a low-contrast target against the background in an event-related design. Half of the runs had a light source surrounding the low-contrast grating for inducing glare. We also studied a healthy control group to account for time-dependent changes and carry-over effects.

We found that glare has a stronger impact over recently operated patients (3 weeks after surgery) than in control subjects. Glare decreases the BOLD signal to low-contrast visual stimuli in the primary visual cortex, which means that patients are more affected by light sources surrounding a visual target. At the third postoperative week, before adaptation occurs, the stimuli was difficult to discern, especially in the presence of a glare source, and therefore the BOLD signal (both the area under the curve and the peak value) was low. As time goes by, a better processing of the visual stimuli was accompanied by better contrast sensitivity and therefore higher BOLD signal in the primary visual cortex. Glare induces a veil of luminance that can be compared to noise. The activation elicited by this "noise" decreased during follow up. Consequently, the signal elicited by the contrast stimulus, despite the presence of the irrelevant stimulus (glare), was higher in the second visit.

Patients also 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, whereas controls only showed deactivations in the occipital lobe, likely related to visibility levels. Patients who were more bothered by visual symptoms showed more activity in the top-down attentional network (parietal and frontal lobes). In addition, they also had increased activity in the cingulate cortex and in the caudate nucleus. The increased activity

of cortical areas dedicated to attention (frontal and parietal lobes), of cortical areas dedicated to learning and cognitive control (cingulate) and to task planning and solving (caudate) likely represent the beginning of the neuroadaptation process.[50-53]

At the 6th month visit, glare no longer significantly decreased visual cortex activation to threshold stimuli, meaning that patients are eventually more able to discriminate low contrast stimuli, despite the presence of glare. This is an objective measure of the improvement of disability glare, at the cortical level. There was also only a relative recruitment of the middle frontal gyrus when patients discriminated very low contrast targets, meaning that less effort-related areas had to be activated for stimuli discrimination. Indeed, previous studies have shown a FMRI response enhancement in the visual cortex associated with the development of expertise in visual tasks, and reduction of effective effort for a preserved level of task efficacy.[50]

At this visit (6 months), there were additionally no significant differences in FMRI activations between high-score (feeling more bothered by dysphopotsia) and low-score (less bothered) groups, in accordance with symptomatic improvement. Again, this likely reflects that patients more bothered by dysphotic symptoms required increased activity of the attentional network at the first visit, which facilitated perceptual learning through an interaction of attention-related and visual cortical regions, leading to a normalization at the second visit.[51]

It has been shown that cortical regions associated with the attentional network are less activated after learning a visual task, and the decrease in brain activation is highly correlated with the magnitude of expertise acquisition and performance improvement.[51] Although there was no visual task training in our experiment, as the visual task was repeated only once at the 6th month follow-up, we can consider every day vision after surgery as a learning experience. Patients are exposed to glare sources and low contrast stimuli on a daily basis, and repeated experience with a visual stimulus can result in improved perception of the stimulus, i.e., perceptual learning.[51] With practice, humans become attuned to the relevant features and, over time, come to extract these with increasing selectivity and fluency.[54] The reduction of activation in attention-related areas during learning may represent a reduced requirement for attention as the task becomes easier due to improved processing efficacy.[50, 51] The cingulate gyrus region has an important role in attention, goal-directed behaviours and error monitoring, which explains its relative activation in the first study visit, when neuroadaptation has just started taking place, but no longer at the second visit, when task performance efficacy is improved.[52]

The same rationale applies to the relative absence of caudate activations in the second visit, as this sub-cortical region is involved in the planning and execution of strategies to attain complex/difficult goals.[53]

Because improvements during follow-up could be attributed to an improvement in optical properties, we performed wavefront analysis with a ray-tracing aberrometer at both study visits. Ray-tracing aberrometers use parallel thin beams in separate and concentric arrays that are projected sequentially onto the eye.[55] This method avoids any data confusion by enabling highly aberrated eyes to be measured on a point-by-point basis.[55] The location on the retina where each entering light beam reflects is sensed by photodetectors. This property is especially useful in the setting of multifocal IOLS, in which other aberrometers tend to have unreliable measurements.[56] Furthermore, the device is equipped with a topographer and its software allows for angle kappa and alpha measurement, as well as the decentration of the IOL from the first Purkinje reflex. It is important to measure and control the eye´s optical properties to ensure that improvement has occurred due to better processing in the brain and not due to an improvement in optical parameters, such as higher-order aberrations, modulation transfer function (MTF) or Strehl ratio. There were no significant changes between visits in total root mean square (RMS), higher-order RMS, average MTF height, MTF for 10 cpd spatial frequencies and Strehl ratio. This fact highlights that the improvements noted in our study were unlikely to be related to optical properties.

We also evaluated if there was an association between optical properties and population receptive fields (PRF). Smaller PRFs reflect more fine-tuned visual processing, effectively increasing the spatial resolution of the visual system, while large PRFs reflect a coarser neural representation of visual space.[57, 58] Our study demonstrated, for the first time, that optical properties of the eye influence PRF sizes and, consequently, cortical resolution of subjects who underwent recently cataract surgery. However, patients with better (smaller) PRF had higher questionnaire scores (more dysphotopsia). Indeed, our results showed a striking dissociation between optical parameters/PRFs and the perceived quality of vision, often even in opposing directions. These findings suggest that a more fine-tuned visual processing (with smaller PRF sizes) may allow more intense perception of dysphotic phenomena (halos around lights, starbusts, glare) and therefore paradoxically worsened subjectively perceived quality of vision. This may explain why there is no correlation between questionnaire scores and optical properties in the literature of the field.

Therefore, this study also shows, for the first time, an association between patients reported subjective difficulties and FMRI outcomes, independently of optical parameters and psychophysical performance. It also provides compelling evidence that neuroadaptation to multifocal IOLs occurs through a process of attentional network, sub-cortical caudate and cingulate recruitment in the initial post-operative period. A form of long-term adaptation/functional plasticity (probably perceptual learning) leads to a regularization of brain activity towards a non-effort neural activation pattern. It is likely that this change in activity represents an increase in neural efficiency such that fewer brain regions are required to perform the tasks, as previously reported for gaining of expertise in computer game tasks.[59]

The immediate application of this work lies in patient reassurement. Patients feeling more bothered by lights may paradoxically have an improved tuning of their visual cortex properties and achieve excellent optical and visual outcomes. In addition, brain activity regularization towards a non-effort pattern will probably occur in the following months after cataract surgery. Moreover, patients should not refrain from using their eyes and performing demanding tasks. They may require additional attentional network activity initially, but we have shown that this activation decreases over time and is accompanied by visual, psychophysical and reading performance improvement. Indeed, attentional network recruitment has been shown to facilitate perceptual learning through an interaction of attention-related and visual cortical regions.[51]

Bridging the gap between optical properties and subjective symptoms may lead to improved treatment of dysphotopsia. Anxiety may have an impact on perceptual learning.[60] Performance declines when resources (e.g.,spatial attention, executive function) devoted to goal-directed behaviors are consumed by anxiety.[60, 61] Anxiety impacts both verbal and spatial processes, as described by correlations between anxiety and performance impairment.[60] Therefore, anxiety may have to be addressed in some post-operative patients. Perceptual training through demanding visual tasks could also help symptomatic patients to select relevant information, ignore noise stimuli, such as halos, and improve low-contrast detection under glare.

Dysphotopsia may also occur with monofocal IOLs, particularly in the early post-operative period. Therefore, our results may be applicable to all IOL adaptations and may not be specific

to multifocal IOLs. It would also be interesting, in the future, to compare adaptation in patients undergoing cataract surgery with monofocal versus multifocal IOL implantation.

In addition, it will be clinically relevant to study neuroadaptation to different IOL designs, as some designs may induce less dysphotopsia and allow a physiological adaptation. This question will be addressed in the continuation of one of the funded projects leading to this thesis. Furthermore, evaluating functional connectivity among visual and attention-related areas would be especially important in patients in which adaptation failed to occur. Specifically, corticostriatal loops contribute to the interpretation of ambiguous visual scenes, which may be the case in the presence of haloes, glare and starbursts.[62] This could lead to the identification of pre-operative markers associated with a positive adaptation to multifocal IOLs and other refractive approaches. Specifically, this knowledge may allow to the development of a visual stress test (inspired by cardiovascular stress tests) for pre-operative use, in which psychophysical and FMRI could be combined to test adaptability to glare and visual attention, despite the presence of distractors.

We look forward to continue this research and contribute to a better understanding of human perceptual construction of adaptive vision.

REFERENCES

1 Nanavaty MA, Wearne MJ. Perioperative Antibiotic Prophylaxis During Phaco-Emulsification and Intraocular Lens Implantation: National Survey of Smaller Eye Units in England. Clin Exp Ophthalmol 2010; 38: 462-466

2 Agresta B, Knorz MC, Kohnen T, Donatti C, Jackson D. Distance and near Visual Acuity Improvement after Implantation of Multifocal Intraocular Lenses in Cataract Patients with Presbyopia: A Systematic Review. J Refract Surg 2012; 28: 426-435

3 Martins Rosa A, Silva MF, Ferreira S, Murta J, Castelo-Branco M. Plasticity in the Human Visual Cortex: An Ophthalmology-Based Perspective. Biomed Res Int 2013; 2013: 568354

4 Kinard K, Jarstad A, Olson RJ. Correlation of Visual Quality with Satisfaction and Function in a Normal Cohort of Pseudophakic Patients. J Cataract Refract Surg 2013; 39: 590-597

5 de Vries NE, Webers CA, Touwslager WR, Bauer NJ, de Brabander J, Berendschot TT, Nuijts RM. Dissatisfaction after Implantation of Multifocal Intraocular Lenses. J Cataract Refract Surg 2011; 37: 859-865

6 Wilkins MR, Allan BD, Rubin GS, Findl O, Hollick EJ, Bunce C, Xing W, Moorfields IOLSG. Randomized Trial of Multifocal Intraocular Lenses Versus Monovision after Bilateral Cataract Surgery. Ophthalmology 2013; 120: 2449-2455 e2441

7 Woodward MA, Randleman JB, Stulting RD. Dissatisfaction after Multifocal Intraocular Lens Implantation. J Cataract Refract Surg 2009; 35: 992-997

8 Welch NR, Gregori N, Zabriskie N, Olson RJ. Satisfaction and Dysphotopsia in the Pseudophakic Patient. Can J Ophthalmol 2010; 45: 140-143

9 Holladay JT, Zhao H, Reisin CR. Negative Dysphotopsia: The Enigmatic Penumbra. J Cataract Refract Surg 2012; 38: 1251-1265

10 Calladine D, Evans JR, Shah S, Leyland M. Multifocal Versus Monofocal Intraocular Lenses after Cataract Extraction. Cochrane Database Syst Rev 2012: CD003169

11 Mamalis N, Brubaker J, Davis D, Espandar L, Werner L. Complications of Foldable Intraocular Lenses Requiring Explantation or Secondary Intervention--2007 Survey Update. J Cataract Refract Surg 2008; 34: 1584-1591

12 Dolders MG, Nijkamp MD, Nuijts RM, van den Borne B, Hendrikse F, Ament A, Groot W. Cost Effectiveness of Foldable Multifocal Intraocular Lenses Compared to Foldable Monofocal Intraocular Lenses for Cataract Surgery. Br J Ophthalmol 2004; 88: 1163-1168

13 Braga-Mele R, Chang D, Dewey S, Foster G, Henderson BA, Hill W, Hoffman R, Little B, Mamalis N, Oetting T, Serafano D, Talley-Rostov A, Vasavada A, Yoo S, Committee ACC. Multifocal Intraocular Lenses: Relative Indications and Contraindications for Implantation. J Cataract Refract Surg 2014; 40: 313-322

14 Fernandez-Buenaga R, Alio JL, Munoz-Negrete FJ, Barraquer Compte RI, Alio-Del Barrio JL. Causes of Iol Explantation in Spain. Eur J Ophthalmol 2012; 22: 762-768

15 Palomino Bautista C, Carmona Gonzalez D, Castillo Gomez A, Bescos JA. Evolution of Visual Performance in 250 Eyes Implanted with the Tecnis Zm900 Multifocal Iol. Eur J Ophthalmol 2009; 19: 762-768

16 Pepin SM. Neuroadaptation of Presbyopia-Correcting Intraocular Lenses. Curr Opin Ophthalmol 2008; 19: 10-12

17 Shimizu K, Ito M. Dissatisfaction after Bilateral Multifocal Intraocular Lens Implantation: An Electrophysiology Study. J Refract Surg 2011; 27: 309-312

18 Rabsilber TM, Rudalevicius P, Jasinskas V, Holzer MP, Auffarth GU. Influence of +3.00 D and +4.00 D near Addition on Functional Outcomes of a Refractive Multifocal Intraocular Lens Model. J Cataract Refract Surg 2013; 39: 350-357

19 McAlinden C, Pesudovs K, Moore JE. The Development of an Instrument to Measure Quality of Vision: The Quality of Vision (Qov) Questionnaire. Invest Ophthalmol Vis Sci 2010; 51: 5537-5545

20 Sabesan R, Yoon G. Visual Performance after Correcting Higher Order Aberrations in Keratoconic Eyes. J Vis 2009; 9: 6 1-10

21 Campbell FW, Green DG. Optical and Retinal Factors Affecting Visual Resolution. J Physiol 1965; 181: 576-593

22 Webster MA, Georgeson MA, Webster SM. Neural Adjustments to Image Blur. Nat Neurosci 2002; 5: 839-840

23 Artal P, Chen L, Fernandez EJ, Singer B, Manzanera S, Williams DR. Neural Compensation for the Eye's Optical Aberrations. J Vis 2004; 4: 281-287

24 Nelson CA. Neural Plasticity and Human Development: The Role of Early Experience in Sculpting Memory Systems. Developmental Science 2000; 3: 115-136

25 Karmarkar UR, Dan Y. Experience-Dependent Plasticity in Adult Visual Cortex. Neuron 2006; 52: 577-585

26 Thompson P, Burr D. Visual Aftereffects. Curr Biol 2009; 19: R11-14

27 Yehezkel O, Sagi D, Sterkin A, Belkin M, Polat U. Learning to Adapt: Dynamics of Readaptation to Geometrical Distortions. Vision Res 2010; 50: 1550-1558

28 Webster MA. Adaptation and Visual Coding. J Vis 2011; 11

29 Werner A, Bayer A, Schwarz G, Zrenner E, Paulus W. Effects of Ageing on Postreceptoral Short-Wavelength Gain Control: Transient Tritanopia Increases with Age. Vision Res 2010; 50: 1641-1648

30 Rivest J, Kim JS, Intriligator J, Sharpe JA. Effect of Aging on Visual Shape Distortion. Gerontology 2004; 50: 142-151

31 Goodyear BG, Menon RS. Effect of Luminance Contrast on Bold Fmri Response in Human Primary Visual Areas. J Neurophysiol 1998; 79: 2204-2207

32 Leonards U, Troscianko T, Lazeyras F, Ibanez V. Cortical Distinction between the Neural Encoding of Objects That Appear to Glow and Those That Do Not. Brain Res Cogn Brain Res 2005; 24: 173-176

33 Malecaze FJ, Boulanouar KA, Demonet JF, Guell JL, Imbert MA. Abnormal Activation in the Visual Cortex after Corneal Refractive Surgery for Myopia: Demonstration by Functional Magnetic Resonance Imaging. Ophthalmology 2001; 108: 2213-2218

34 Kalia A, Lesmes LA, Dorr M, Gandhi T, Chatterjee G, Ganesh S, Bex PJ, Sinha P. Development of Pattern Vision Following Early and Extended Blindness. Proc Natl Acad Sci U S A 2014; 111: 2035-2039

35 Sabel BA, Gudlin J. Vision Restoration Training for Glaucoma: A Randomized Clinical Trial. JAMA Ophthalmol 2014; 132: 381-389

36 Baker CI, Peli E, Knouf N, Kanwisher NG. Reorganization of Visual Processing in Macular Degeneration. J Neurosci 2005; 25: 614-618

37 Wilkins MR, Allan BD, Rubin GS, Findl O, Hollick EJ, Bunce C, Xing W. Randomized Trial of Multifocal Intraocular Lenses Versus Monovision after Bilateral Cataract Surgery. Ophthalmology 2013; 120: 2449-2455 e2441

38 Huettel SA, Song AW, McCarthy G. Functional Magnetic Resonance Imaging. Sinauer Associates, Incorporated, 2009

39 Pauling L, Coryell CD. The Magnetic Properties and Structure of Hemoglobin, Oxyhemoglobin and Carbonmonoxyhemoglobin. Proc Natl Acad Sci U S A 1936; 22: 210-216

40 Miki A, Haselgrove JC, Liu GT. Functional Magnetic Resonance Imaging and Its Clinical Utility in Patients with Visual Disturbances. Surv Ophthalmol 2002; 47: 562-579

41 Goodyear BG, Nicolle DA, Humphrey GK, Menon RS. Bold Fmri Response of Early Visual Areas to Perceived Contrast in Human Amblyopia. J Neurophysiol 2000; 84: 1907-1913

42 Kontsevich LL, Tyler CW. Bayesian Adaptive Estimation of Psychometric Slope and Threshold. Vision Res 1999; 39: 2729-2737

43 Montes-Mico R, Alio JL. Distance and near Contrast Sensitivity Function after Multifocal Intraocular Lens Implantation. J Cataract Refract Surg 2003; 29: 703-711

44 Rosa AM, Loureiro Silva MF, Lobo C, Mira JB, Farinha CL, Povoa JA, Castelo-Branco M, Murta JN. Comparison of Visual Function after Bilateral Implantation of Inferior Sector-Shaped near-Addition and Diffractive-Refractive Multifocal Iols. J Cataract Refract Surg 2013; 39: 1653-1659

45 Radner W, Obermayer W, Richter-Mueksch S, Willinger U, Velikay-Parel M, Eisenwort B. The Validity and Reliability of Short German Sentences for Measuring Reading Speed. Graefes Arch Clin Exp Ophthalmol 2002; 240: 461-467

46 Rosa AM, Farinha CL, Radner W, Diendorfer G, Loureiro MF, Murta JN. Development of the Portuguese Version of a Standardized Reading Test: The Radner-Coimbra Charts. Arq Bras Oftalmol 2016; 79: 238-242

47 Elliott DB, Hurst MA, Weatherill J. Comparing Clinical Tests of Visual Function in Cataract with the Patient's Perceived Visual Disability. Eye (Lond) 1990; 4 (Pt 5): 712-717

48 Alio JL, Radner W, Plaza-Puche AB, Ortiz D, Neipp MC, Quiles MJ, Rodriguez-Marin J. Design of Short Spanish Sentences for Measuring Reading Performance: Radner-Vissum Test. J Cataract Refract Surg 2008; 34: 638-642

49 Khadka J, McAlinden C, Pesudovs K. Quality Assessment of Ophthalmic Questionnaires: Review and Recommendations. Optom Vis Sci 2013; 90: 720-744

50 Lewis CM, Baldassarre A, Committeri G, Romani GL, Corbetta M. Learning Sculpts the Spontaneous Activity of the Resting Human Brain. Proc Natl Acad Sci U S A 2009; 106: 17558-17563

51 Mukai I, Kim D, Fukunaga M, Japee S, Marrett S, Ungerleider LG. Activations in Visual and Attention-Related Areas Predict and Correlate with the Degree of Perceptual Learning. J Neurosci 2007; 27: 11401-11411

52 Choi MH, Kim HS, Yoon HJ, Lee JC, Baek JH, Choi JS, Tack GR, Min BC, Lim DW, Chung SC. Increase in Brain Activation Due to Sub-Tasks During Driving: Fmri Study Using New Mr-Compatible Driving Simulator. J Physiol Anthropol 2017; 36: 11

53 Grahn JA, Parkinson JA, Owen AM. The Cognitive Functions of the Caudate Nucleus. Prog Neurobiol 2008; 86: 141-155

54 Kellman PJ, Garrigan P. Perceptual Learning and Human Expertise. Phys Life Rev 2009; 6: 53-84

55 Molebny VV, Panagopoulou SI, Molebny SV, Wakil YS, Pallikaris IG. Principles of Ray Tracing Aberrometry. J Refract Surg 2000; 16: S572-575

56 Jun I, Choi YJ, Kim EK, Seo KY, Kim TI. Internal Spherical Aberration by Ray Tracing-Type Aberrometry in Multifocal Pseudophakic Eyes. Eye (Lond) 2012; 26: 1243-1248

57 Song C, Schwarzkopf DS, Kanai R, Rees G. Neural Population Tuning Links Visual Cortical Anatomy to Human Visual Perception. Neuron 2015; 85: 641-656

58 Harvey BM, Dumoulin SO. The Relationship between Cortical Magnification Factor and Population Receptive Field Size in Human Visual Cortex: Constancies in Cortical Architecture. J Neurosci 2011; 31: 13604-13612

59 Sigman M, Pan H, Yang Y, Stern E, Silbersweig D, Gilbert CD. Top-Down Reorganization of Activity in the Visual Pathway after Learning a Shape Identification Task. Neuron 2005; 46: 823-835

60 Vytal KE, Cornwell BR, Letkiewicz AM, Arkin NE, Grillon C. The Complex Interaction between Anxiety and Cognition: Insight from Spatial and Verbal Working Memory. Front Hum Neurosci 2013; 7: 93

61 Shackman AJ, Maxwell JS, McMenamin BW, Greischar LL, Davidson RJ. Stress Potentiates Early and Attenuates Late Stages of Visual Processing. J Neurosci 2011; 31: 1156-1161

62 Lopez-Paniagua D, Seger CA. Interactions within and between Corticostriatal Loops During Component Processes of Category Learning. J Cogn Neurosci 2011; 23: 3068-3083

SUPPLEMENTS

SUPPLEMENT 1 – PROTOCOL APPROVAL: COMISSÃO NACIONAL DE PROTEÇÃO DE DADOS

COMISSÃO NACIONAL
DE PROTECÇÃO DE DADOS

AUTORIZAÇÃO N.º 6440 /2015

I. Pedido

A **Faculdade de Medicina da Universidade de Coimbra**, através do Instituto de Imagem Biomédica e Ciências da Vida (IBILI) notificou à Comissão Nacional de Protecção de Dados (CNPD) um tratamento de dados pessoais com a finalidade de elaborar um estudo intitulado "Plasticidade no Cortex Visual do Adulto após Cirurgia de Catarata e Refrativa".

Trata-se de investigação destinada a aprofundar o conhecimento das interações olho-cérebro, em particular após cirurgia de catarata com lente intra-ocular multifocal.

A amostra do estudo será constituída um número de 40 doentes com indicação para cirurgia de catarata/presbiopia e 20 doentes sem essa indicação, seguidos no IBILI.

A participação no estudo consistirá na recolha de dados pela equipa de investigação, através de exame à acuidade visual, testes psicofísicos, tomografia de coerência ótica, perimetria estática computorizada, exame de ressonância magnética e questionário para avaliação da função visual.

Será solicitado consentimento informado aos participantes.

Os dados serão recolhidos num caderno de recolha de dados no qual não há identificação nominal do titular, sendo aposto um código de participante. A chave desta codificação só será conhecida da equipa de investigação.
Os destinatários serão ainda informados sobre a natureza facultativa da sua participação e será garantida confidencialidade no tratamento.

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II. **Análise**

A CNPD já se pronunciou na sua Deliberação n.º 227/2007 sobre o enquadramento legal, os fundamentos de legitimidade, os princípios orientadores para o correto cumprimento da LPD, bem como as condições gerais aplicáveis ao tratamento de dados pessoais para a finalidade de estudos de investigação na área da saúde.
Porque em grande parte referentes à vida privada e também à saúde, os dados recolhidos pela requerente têm a natureza de sensíveis, nos termos do disposto no n.º 1 do artigo 7.º da LPD.

Em regra, o tratamento de dados sensíveis é proibido, de acordo com o disposto no n.º 1 do artigo 7.º da LPD. Todavia, nos termos do n.º 2 do mesmo artigo, o tratamento de dados da vida privada e de saúde é permitido, quando haja uma disposição legal que consagre esse tratamento de dados, quando por motivos de interesse público importante o tratamento for indispensável ao exercício das atribuições legais ou estatutárias do seu responsável ou quando o titular dos dados tiver prestado o seu consentimento.

Não estando preenchidas as duas primeiras condições de legitimidade, o fundamento de legitimidade só pode basear-se no consentimento dos titulares dos dados ou dos representantes legais, quando os titulares dos dados sejam incapazes.

Assim, é necessário o «consentimento expresso do titular», entendendo-se por consentimento qualquer manifestação de vontade, livre, específica e informada, nos termos da qual o titular aceita que os seus dados sejam objeto de tratamento (cf. artigo 3.º, alínea *h*), da LPD), o qual deve ser obtido através de uma "declaração de consentimento informado" onde seja utilizada uma linguagem clara e acessível.
Nos termos do artigo 10.º da LPD, a declaração de consentimento tem de conter a identificação do responsável pelo tratamento e a finalidade do tratamento, devendo

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ainda conter informação sobre a existência e as condições do direito de acesso e de retificação por parte do respetivo titular.

Os titulares dos dados, de acordo com a declaração de consentimento informado junta aos autos, apõem as suas assinaturas na mesma, deste modo satisfazendo as exigências legais.

Cabe ao Investigador assegurar a confidencialidade dos dados pessoais e da informação tratada, conforme o estatuído na alínea *g*) do artigo 10.º da Lei n.º 21/2014, de 16 de abril (Lei da investigação clínica).
Assim, apenas poderão ter acesso aos registos médicos originais o médico assistente e um monitor, (nos termos do artigo 11.º da Lei da investigação clínica), e apenas na medida do estritamente necessário, também recaindo sobre este a obrigação de confidencialidade.

A informação tratada é recolhida de forma lícita (artigo 5.º, n.º1 alínea *a*) da Lei n.º 67/98), para finalidades determinadas, explícitas e legítimas (cf. alínea *b*) do mesmo artigo) e não é excessiva.

O fundamento de legitimidade é o consentimento expresso do titular dos dados.

III. Conclusão

Assim, nos termos das disposições conjugadas do n.º 2 do artigo 7.º, n.º 1 do artigo 27.º, alínea a) do n.º 1 do artigo 28.º e artigo 30.º da LPD, com as condições e limites fixados na referida Deliberação n.º 227/2007, que se dão aqui por reproduzidos e que fundamentam esta decisão, autoriza-se o tratamento de dados *supra* referido, para a elaboração do presente estudo, consignando-se o seguinte:

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Responsável pelo tratamento: Faculdade de Medicina da Universidade de Coimbra, através do Instituto de Imagem Biomédica e Ciências da Vida (IBILI);
Finalidade: estudo intitulado "Plasticidade no Cortex Visual do Adulto após Cirurgia de Catarata e Refrativa";
Categoria de Dados pessoais tratados: Número do doente; Profissão desempenhada a maior parte da vida; grau de escolaridade; data de início da mesma ocupação; atualmente ativo ou reformado; estado civil. História clínica médica geral: doenças neurológicas (esclerose múltipla, cefaleias, Parkinson) acidentem vascular isquémico (sim/não, ano de diagnóstico). Medicação habitual: lista de medicação habitual. Para cada fármaco, dose, frequência, data de início e de fim. História clínica oftalmológica: cirurgias intra-oculares (data, tipo de cirurgia), outras doenças oftalmológicas que não a catarata; colírios atualmente prescritos (sim/não, olho, nome, frequência, data de início). Questionário de qualidade visual: presença de sintomas, frequência, intensidade e incómodo dos mesmos (halos, brilhos, riscos estrelados, visão enevoada, visão desfocada, visão distorcida, visão dupla/múltipla). Exame oftalmológico: acuidade visual não corrigida e corrigida para perto, distância intermédia e longe; refração e adição para perto se necessário; biomicroscopia; pressão intra-ocular; exame do fundo do olho. Teste de velocidade de leitura monocular e binocular. Exames de imagem: tomografia de coerência óptica (OCT), topografia da córnea e aberrometria, *scatter* de luz intraocular. Exames psicofísicos: sensibilidade ao contraste com e sem fonte de encadeamento. Exames de ressonância magnética funcional: sinal BOLD obtido mediante a apresentação de estímulos visuais (*Gabor gratings*: linhas verticais com contraste variável) com e sem fonte de encadeamento.
Entidades a quem podem ser comunicados: Não há.
Formas de exercício do direito de acesso e retificação: Junto do médico investigador;
Interconexões de tratamentos: Não há.
Transferências de dados para países terceiros: Não há.
Prazo de conservação: A chave de codificação dos dados deve ser destruída um mês após o fim do estudo.

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Dos termos e condições fixados na presente Autorização decorrem obrigações que o responsável deve cumprir. Deve, igualmente, dar conhecimento dessas condições a todos os intervenientes no circuito de informação.

Lisboa, 7 de julho de 2015

Filipa Calvão (Presidente)

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SUPPLEMENT 2 – PROTOCOL APPROVAL: COMISSÃO DE ÉTICA

· U C ·

FMUC FACULDADE DE MEDICINA
UNIVERSIDADE DE COIMBRA

COMISSÃO DE ÉTICA DA FMUC

Of. Refª **025-CE-2014**
Data 28/4/**2014**

C/conhecimento ao aluno

Exmo Senhor
Prof. Doutor Joaquim Neto Murta
Presidente do Conselho Científico

Assunto: Projecto de Investigação no âmbito do Programa de Doutoramento em Ciências da Saúde. (refª CE-015/2014)

Candidato(a): Andreia de Faria Martins Rosa

Título do Projecto: "*Plasticidade no córtex visual do adulto após cirurgia refrativa e de catarata*".

A Comissão de Ética da Faculdade de Medicina, após análise do projecto de investigação supra identificado, decidiu emitir o parecer que a seguir se transcreve: ***"Parecer Favorável".***

Queira aceitar os meus melhores cumprimentos.

O Presidente,

Prof. Doutor João Manuel Pedroso de Lima

GC

SERVIÇOS TÉCNICOS DE APOIO À GESTÃO - STAG • COMISSÃO DE ÉTICA
Pólo das Ciências da Saúde • Unidade Central
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E-mail: comissaoetica@fmed.uc.pt | www.fmed.uc.pt

SUPPLEMENT 3 - INFORMED CONSENT

Instituto de Imagem Biomédica e Ciências da Vida
Instituto Multidisciplinar de Investigação | Faculdade de Medicina da Universidade de Coimbra

FORMULÁRIO DE INFORMAÇÃO AO PARTICIPANTE
- CONSENTIMENTO INFORMADO –

TÍTULO DO PROJECTO DE INVESTIGAÇÃO

PLASTICIDADE NO CORTEX VISUAL DO ADULTO APÓS CIRURGIA DE CATARATA E REFRATIVA
Plasticity in the adult visual cortex after cataract and refractive surgery

PROTOCOLO
Não aplicável

PROMOTOR
Instituto de Imagem Biomédica e Ciências da Vida (IBILI), Faculdade de Medicina da Universidade de Coimbra (FMUC)

INVESTIGADOR COORDENADOR
Professor Doutor Joaquim Neto Murta e Professor Doutor Miguel Castelo-Branco

CENTRO DE ESTUDO
IBILI, FMUC

INVESTIGADOR PRINCIPAL
Drª Andreia de Faria Martins Rosa

MORADA
IBILI, Faculdade de Medicina da Universidade Coimbra
Azinhaga de Santa Comba, Celas, 3000-548 Coimbra

CONTACTO TELEFÓNICO
239 480261

NOME DO PARTICIPANTE(LETRA DE IMPRENSA)

É convidado(a) a participar voluntariamente neste estudo porque tem catarata/ presbiopia (diminuição da visão para perto ou de leitura sem óculos) e vai ser operado ou tem catarata/ presbiopia, mas ainda não necessita de cirurgia.
Este procedimento, designado por Consentimento Informado, descreve a finalidade do Estudo, os procedimentos, os possíveis benefícios e riscos. A sua participação poderá

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contribuir para melhorar os resultados visuais obtidos após cirurgia de catarata/ presbiopia.
Receberá uma cópia deste Consentimento Informado para rever e/ou solicitar aconselhamento de familiares e amigos. O Investigador ou outro membro da sua equipa irá esclarecer qualquer dúvida que tenha sobre o termo de consentimento e também alguma informação que possa não ter compreendido.
Deve tomar a decisão de participar ou não neste estudo depois de o compreender e de não ter qualquer dúvida acerca do mesmo. Caso queira participar, ser-lhe-á solicitado que assine e date este formulário. Após a sua assinatura e a do Investigador, ser-lhe-á entregue uma cópia. Caso não queira participar, não haverá qualquer penalização nos cuidados que irá receber.

1. INFORMAÇÃO GERAL E OBJECTIVOS DO ESTUDO

Este estudo irá decorrer no Instituto de Imagem Biomédica e Ciências da Vida (IBILI) da Faculdade de Medicina da Universidade de Coimbra (FMUC) e tem como objetivo aprofundar o conhecimento das interações olho-cérebro, em particular após cirurgia de catarata com lente intra-ocular multifocal. Mais especificamente, pretendemos compreender os mecanismos pelos quais o cérebro se adapta às mudanças na formação da imagem. Na cirurgia de catarata é removido o cristalino opaco e é colocada uma lente dentro do olho. As lentes tradicionais (monofocais) só permitem focar a imagem de longe, necessitando de óculos para perto. As lentes mais recentes (multifocais) focam a imagem de longe e de perto, evitando assim o uso de óculos para a maioria das atividades diárias. Esta maneira diferente de formar a imagem pode levar ao aparecimento de brilhos e halos à volta das luzes, que costumam desaparecer nos primeiros 6 meses após a cirurgia. Não se sabe como é que o cérebro processa esta adaptação e é isso que pretendemos descobrir. Para isso é necessário fazer testes psicofísicos (testes em que se pede para reconhecer letras, para ver luzes e barras de cor cinzenta) e ressonância magnética funcional. Não há exposição a radiação ionizante e é sempre efetuado um questionário de segurança para excluir as situações em que a exposição a campos magnéticos possa ser um risco para o participante. Não são efetuados quaisquer estudos invasivos, nomeadamente a injeção de qualquer produto de contraste. Trata-se de um estudo observacional, pelo que não será feita nenhuma alteração nas suas rotinas diárias ou tratamentos habituais.

Este estudo foi aprovado pela Comissão de Ética da FMUC de modo a garantir a protecção dos direitos, segurança e bem-estar de todos os doentes e outros participantes incluídos e garantir prova pública dessa proteção.
Como participante neste estudo, beneficiará da vigilância institucional e encaminhamento adequado, garantindo assim a sua segurança.
Este estudo é composto por três visitas de, aproximadamente, duas horas (dependendo do número de exames a realizar).

Instituto de Imagem Biomédica e Ciências da Vida
Instituto Multidisciplinar de Investigação | Faculdade de Medicina da Universidade de Coimbra

Está prevista a inclusão de cerca de 40 doentes com indicação para cirurgia de catarata/ presbiopia e 20 doentes sem indicação para cirurgia de catarata/ presbiopia.

2. PROCEDIMENTOS E CONDUÇÃO DO ESTUDO

2.1. Procedimentos

Se fizer parte deste estudo, ser-lhe-á solicitado que colabore na realização de um conjunto de testes não invasivos, alguns dos quais utilizados na prática clínica e outros desenvolvidos recentemente. Estes procedimentos serão realizados por uma equipa de técnicos especializados que integram a equipa de investigação deste Estudo, terão a duração máxima de 2 horas.

Exame oftalmológico

Será efetuado um exame à acuidade visual, para verificar a qualidade da sua visão nos dois olhos. A sua visão será avaliada para várias distâncias (perto ou leitura, intermédia ou computador e de longe).

Testes psicofísicos

Estes testes consistem em avaliar a sensibilidade ao contraste (a capacidade de distinguir objetos semelhantes ao fundo onde estão) com e sem fonte luminosa para produzir encadeamento. Terá apenas que carregar num botão sempre que vir a imagem em estudo. Estes testes serão efetuados nas 2 visitas após a cirurgia, caso tenha sido operado, ou nas 2 visitas após a visita de inclusão, caso não tenha sido operado.

Tomografia de Coerência Óptica - OCT

Feixes de luz serão enviados através da sua pupila com o uso de um aparelho dedicado. Estes feixes de luz permitem a visualização de camadas da retina. Esta técnica de imagem é não invasiva e permite a medição (indireta) da espessura da retina. Este exame será feito apenas antes da cirurgia (ou na visita de inclusão), para excluir patologia na retina que possa interferir com os objetivos do estudo.

Perimetria estática computorizada

Este exame consiste em ver pequenos pontos de luz de intensidade variável em várias localizações do campo visual. Será apenas necessário pressionar um botão quando vir os pontos de luz. Este exame será feito apenas antes da cirurgia (ou na visita de inclusão), para excluir patologia no nervo ótico/ via ótica/ córtex visual que possa interferir com os objetivos do estudo.

Questionário

Questionário validado para avaliação da função visual, a ser preenchido nas 2 visitas após a cirurgia (ou nas 2 visitas após a visita de inclusão).

Exame de Ressonância Magnética

Efetuada nas 2 visitas após a cirurgia (ou nas 2 visitas após a visita de inclusão).
A duração total, com preparação e preenchimento de Questionário de Segurança é de aproximadamente 1h.
A técnica de Ressonância Magnética (RM) é uma técnica não invasiva e que não comporta nenhum risco para o participante.
Antes de efetuar qualquer exame por RM é realizado um Questionário de Segurança por técnicos de RM (assegurando que não é portador de implantes metálicos amovíveis entre outras situações incompatíveis, maximizando a sua segurança). Depois, deitar-se-á numa mesa que deslizará (até cerca de metade do corpo) para o interior de uma câmara aberta (máquina de RM), onde será realizado o exame.
Note-se que a RM só será feita em condições que permitam a colaboração do participante, não sendo utilizado qualquer tipo de anestesia, ou a injeção de agentes de contraste.

Estudo de MRI - Neste exame terá apenas que se manter relaxado e imóvel dentro da máquina da RM enquanto são feitas as aquisições de informação. Este exame permite obter imagens (como fotografias) do cérebro.

Estudo de fMRI - Este exame é apenas um subtipo de aquisição de imagem de RM, no qual será dada uma tarefa ao participante que está dentro da máquina. Este exame permite estudar as propriedades das diferentes áreas do cérebro envolvidas na visão e que estão ativas durante a realização da tarefa.

2.2. Calendário das visitas/ Duração
Este estudo consiste em 3 visitas com duração de cerca de 2 horas. De seguida é feita uma descrição do estudo:

Visita pré-operatória/ Visita baseline dos doentes que não necessitam de cirurgia

Exame oftalmológico
Não invasivo

Tomografia de Coerência Óptica – OCT
Não invasivo

Perimetria estática computorizada
Não invasivo

Visitas pós-operatórias/ Visitas subsequentes dos doentes não operados

Exame oftalmológico
Não invasivo

Instituto de Imagem Biomédica e Ciências da Vida
Instituto Multidisciplinar de Investigação | Faculdade de Medicina da Universidade de Coimbra

Testes psicofísicos (avaliação dos vários componentes da função visual)
Não invasivo

Exame de Ressonância Magnética
Não invasivo
- Estudo de MRI
- Estudo de fMRI

Serão feitas perguntas a respeito da sua história médica e da medicação que toma.

2.3. Tratamento de dados/Randomização
Não serão realizados quaisquer tratamentos no âmbito deste estudo.

3. RISCOS E POTENCIAIS INCONVENIENTES PARA O DOENTE
Todos os testes indicados e que são parte do estudo são testes de rotina utilizados no trabalho experimental e/ou prática clínica. Todos os equipamentos têm marcação UE e são utilizados para o uso em Seres Humanos. Os testes efetuados são não invasivos, não comportando qualquer perigo para a saúde dos participantes. Relativamente à Ressonância Magnética: 1) Este exame não expõe o participante a radiações ionizantes; 2) Previamente à realização do estudo, é efetuado um Questionário de Segurança que permite excluir as situações em que a exposição a campos magnéticos representa uma situação de risco para o participante (ver questionário anexo); 3) Não serão efetuados quaisquer estudos invasivos, nomeadamente a injeção de qualquer produto de contraste ou anestesia. Será fornecido um botão de emergência, sendo o exame interrompido assim que este seja pressionado. O Investigador(a) responsável pela realização do estudo estará em contacto permanente consigo.

4. POTENCIAIS BENEFÍCIOS
Este estudo tem a vantagem de estudar com detalhe os mecanismos de adaptação do cérebro e permitir um melhor conhecimento da progressão dos mesmos. Além disso, a informação que será recolhida irá contribuir para uma melhor informação dos investigadores, médicos e outros técnicos de saúde, de forma a melhorar os cuidados clínicos, bem como no desenho de novas estratégias terapêuticas.

5. NOVAS INFORMAÇÕES
Será alertado de qualquer nova informação que possa ser relevante para a sua condição e/ou que possa influenciar a sua vontade de continuar a participar no Estudo.

6. TRATAMENTOS ALTERNATIVOS
Não receberá qualquer tratamento no contexto do Estudo em que irá participar.

7. SEGURANÇA

Instituto de Imagem Biomédica e Ciências da Vida
Instituto Multidisciplinar de Investigação | Faculdade de Medicina da Universidade de Coimbra

Embora não se espere que venha a sofrer problemas de saúde devidos à sua participação, se sofrer alguma lesão física como resultado de quaisquer procedimentos do estudo, realizados de acordo com o protocolo, será reembolsado pelas despesas médicas necessárias para as tratar. Todos os procedimentos são revistos pelo corpo técnico e todos os incidentes reportados às pessoas e/ou entidades competentes.

8. PARTICIPAÇÃO/ABANDONO VOLUNTÁRIO

É importante que saiba que a decisão de participar neste estudo de investigação é inteiramente voluntária. Pode livremente aceitar ou recusar participar, ou ainda retirar o seu consentimento em qualquer altura sem qualquer consequência para si, sem precisar de explicar as razões, sem qualquer penalidade ou perda de benefícios e sem comprometer a sua relação com o Investigador(a) que lhe propõe a participação neste estudo. Ser-lhe-á pedido para informar o Investigador(a) se decidir retirar o seu consentimento.

O Investigador(a) do estudo pode decidir terminar a sua participação neste estudo se entender que não é do melhor interesse para o seu bem-estar (ou para a sua saúde) continuar nele. A sua participação pode ser também terminada se não estiver a seguir o plano do estudo, por decisão administrativa ou decisão da Comissão de Ética. O Investigador(a) do estudo notificá-lo-á se surgir uma dessas circunstâncias, e falará consigo a respeito da mesma.

9. CONFIDENCIALIDADE

Sem violar as normas de confidencialidade, serão atribuídos a auditores e autoridades reguladoras acesso aos registos médicos para verificação dos procedimentos realizados e informação obtida no estudo, de acordo com as leis e regulamentos aplicáveis. Os seus registos manter-se-ão confidenciais e anonimizados de acordo com os regulamentos aplicáveis. Se os resultados deste estudo forem publicados, a sua identidade manter-se-á confidencial.

Ao assinar este consentimento informado autoriza este acesso condicionado e restrito.

Pode ainda, em qualquer altura, exercer o seu direito de acesso à informação. Pode ter também acesso à sua informação médica/biomédica/resultados dos testes através do Investigador(a) deste estudo. Tem também o direito de se opor à transmissão de dados que sejam cobertos pela confidencialidade profissional.

Os registos médicos que o identificarem e o formulário de Consentimento Informado que assinar serão verificados para fins do estudo pelo promotor e/ou por representantes do promotor, e para fins regulamentares pelo Promotor e/ou pelos representantes do promotor e agências reguladoras noutros países. A Comissão de Ética responsável pelo estudo pode solicitar o acesso aos seus registos médicos para assegurar-se que o estudo está a ser realizado de acordo com o protocolo.

Não pode ser garantida confidencialidade absoluta devido à necessidade de passar a informação a essas partes.

Instituto de Imagem Biomédica e Ciências da Vida
Instituto Multidisciplinar de Investigação | Faculdade de Medicina da Universidade de Coimbra

Ao assinar este termo de Consentimento Informado, permite que as suas informações médicas neste estudo sejam verificadas, processadas e relatadas conforme for necessário para finalidades científicas legítimas.

Confidencialidade e tratamento de dados pessoais

Os dados pessoais dos participantes no Estudo, incluindo a informação médica ou de saúde recolhida ou criada como parte do estudo, (tais como registos médicos ou resultados de testes), serão utilizados para condução do estudo, designadamente para fins de investigação científica e relacionados com a(s) patologia(s) em estudo.
Ao dar o seu consentimento à participação no Estudo, a informação a si respeitante, designadamente a informação experimental/clínica, será utilizada da seguinte forma:

1. O promotor, os investigadores e as outras pessoas envolvidas no estudo recolherão e utilizarão os seus dados pessoais para as finalidades acima descritas.
2. Os dados do estudo, associados às suas iniciais ou a outro código que não o(a) identifica directamente (e não ao seu nome) serão comunicados pelos investigadores e/ou outras pessoas envolvidas no estudo ao promotor do estudo, que os utilizará para as finalidades acima descritas.
3. Os dados do estudo, associados às suas iniciais ou a outro código que não permita identificá-lo(a) directamente, poderão ser comunicados a autoridades de saúde nacionais e internacionais.
4.A sua identidade não será revelada em quaisquer relatórios ou publicações resultantes deste estudo.
5.Todas as pessoas ou entidades com acesso aos seus dados pessoais estão sujeitas a sigilo profissional.
6. Ao dar o seu consentimento para participar no estudo autoriza o Promotor ou empresas de monitorização de estudos, especificamente contratadas para o efeito e seus colaboradores e/ou autoridades de saúde, a aceder aos dados constantes do seu processo clínico, para conferir a informação recolhida e registada pelos investigadores, designadamente para assegurar o rigor dos dados que lhe dizem respeito e para garantir que o estudo se encontra a ser desenvolvido correctamente e que os dados obtidos são fiáveis.
7. Nos termos da lei, tem o direito de, através de um dos médicos envolvidos no estudo, solicitar o acesso aos dados que lhe digam respeito, bem como de solicitar a retificação dos seus dados de identificação.
8.Tem ainda o direito de retirar este consentimento em qualquer altura através da notificação ao Investigador(a), o que implicará que deixe de participar no estudo. No entanto, os dados recolhidos ou criados como parte do estudo até essa altura que não o(a) identifiquem poderão continuar a ser utilizados para o propósito do Estudo, nomeadamente para manter a integridade científica do estudo, e a sua informação médica não será removida do arquivo do estudo.

Instituto de Imagem Biomédica e Ciências da Vida
Instituto Multidisciplinar de Investigação | Faculdade de Medicina da Universidade de Coimbra

9. Se não der o seu consentimento, assinando este documento, não poderá participar neste estudo. Se o consentimento agora prestado não for retirado e até que o faça, este será válido e manter-se-á em vigor.

10. COMPENSAÇÃO
Este é um estudo da iniciativa do Investigador(a) e, por isso, não haverá lugar a qualquer compensação financeira para a elaboração e execução deste para os investigadores, o centro de estudo e os participantes.

11. CONTACTOS
Se tiver perguntas relativas aos seus direitos como participante deste Estudo, deve contactar:

Presidente da Comissão de Ética da FMUC,
Azinhaga de Santa Comba, Celas - 3000-548 Coimbra Contacto telefónico: 239 857 707
e-mail: comissaoetica@fmed.uc.pt

Se tiver questões sobre este Estudo deve contactar:
Investigadores coordenadores: Professor Doutor Joaquim Murta e Professor Doutor Miguel Castelo-Branco
Investigador Principal: Drª Andreia de Faria Martins Rosa
IBILI, Faculdade de Medicina da Universidade de Coimbra
Azinhaga de Santa Comba, Celas, 3000-548 Coimbra Contacto telefónico: 239 480 26

NÃO ASSINE ESTE FORMULÁRIO DE CONSENTIMENTO INFORMADO A MENOS QUE TENHA TIDO A OPORTUNIDADE DE PERGUNTAR E TER RECEBIDO RESPOSTAS SATISFATÓRIAS A TODAS AS SUAS PERGUNTAS.

Instituto de Imagem Biomédica e Ciências da Vida
Instituto Multidisciplinar de Investigação | Faculdade de Medicina da Universidade de Coimbra

CONSENTIMENTO INFORMADO

De acordo com a Declaração de Helsínquia da Associação Médica Mundial e suas atualizações:

1. Declaro ter lido este formulário e aceito de forma voluntária participar neste estudo.
2. Fui devidamente informado(a) da natureza, objetivos, riscos, duração provável do estudo, bem como do que é esperado da minha parte.
3.Tive a oportunidade de fazer perguntas sobre o estudo e percebi as respostas e as informações que me foram dadas. A qualquer momento posso fazer mais perguntas ao médico responsável do estudo.
Durante o estudo e sempre que quiser, posso receber informação sobre o seu desenvolvimento. O médico responsável dará toda a informação importante que surja durante o estudo que possa alterar a minha vontade de continuar a participar.
4. Aceito que utilizem a informação relativa à minha história clínica e os meus tratamentos no estrito respeito do segredo médico e anonimato. Os meus dados serão mantidos estritamente confidenciais. Autorizo a consulta dos meus dados apenas por pessoas designadas pelo promotor e por representantes das autoridades reguladoras.
5. Aceito seguir todas as instruções que me forem dadas durante o estudo. Aceito colaborar com o médico e informá-lo(a) imediatamente das alterações do meu estado de saúde e bem-estar e de todos os sintomas inesperados e não usuais que ocorram.
6. Autorizo o uso dos resultados do estudo para fins exclusivamente científicos e, em particular, aceito que esses resultados sejam divulgados às autoridades sanitárias competentes.
7.Aceito que os dados gerados durante o estudo sejam informatizados pelo promotor ou outrem por si designado.
Eu posso exercer o meu direito de retificação e/ ou oposição.
8. Tenho conhecimento que sou livre de desistir do estudo a qualquer momento, sem ter de justificar a minha decisão e sem comprometer a qualidade dos meus cuidados médicos. Eu tenho conhecimento que o médico tem o direito de decidir sobre a minha saída prematura do estudo e que me informará da causa da mesma.
9. Fui informado que o estudo pode ser interrompido por decisão do investigador, do promotor ou das autoridades reguladoras.

Instituto de Imagem Biomédica e Ciências da Vida
Instituto Multidisciplinar de Investigação | Faculdade de Medicina da Universidade de Coimbra

Nome do Participante ou Representante Legal

Assinatura: _____
Data:_____/_____/ ____

Confirmo que expliquei ao participante acima mencionado a natureza, os objetivos e os potenciais riscos do Estudo acima mencionado.

Nome do Investigador

Assinatura: _____
Data:_____/_____/ ____