Qualitative assessment of visual impairment in patients with age related macular degeneration using standardized, image based questionnaires

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Abstract:	The purpose of the study is to test a simple approach for characterizing subjective perception in patients with choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD). This multicenter study was performed in four private ophthalmology praxes including 20 patients with CNV. Subjects were presented the original image on the affected eye and afterwards modified candidate images to the contralateral eye. Then they chose one image that most closely matched the perception on the affected eye. This was repeated with three different images representing three every day life scenes manipulated to mimic visual perception with reduced color perception (image 1), central scotomas (image 2), and blurring with four varying sizes (image 3). The frequency of response to the forced choice questionnaire experiment for each image was recorded. Our results show that images manipulated using a Gaussian blur filter, a brightness filter and a sinusoidal distortion filter were selected by 9, 10 and 1 patients, respectively. Size of modification was not associated with visual acuity in image 1 or image 3. In image 2, however, the size of the modification was dependent on visual acuity ($p = 0.01$). In conclusion, subjective perception in patients with AMD may significantly differ between individual patients. A better understanding of the visual disturbance will facilitate communication and involvement of patients in treatment decisions.

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Introduction

Age related macular degeneration (AMD) is one of the most common reasons for visual impairment in the Western World.(Colijn et al., 2017) Given that AMD is a disease occurring only in the elderly, this represents a growing socioeconomic challenge especially in industrialized countries. From a pathogenetic point of view, AMD develops in two distinct forms: “dry” AMD, which is characterized by a progressing atrophy of the central retina and neovascular form, where newly developed choroidal vessels (choroidal neovascularisation, CNV) lead to central bleedings, oedema and concomitant vision loss.(Schmidt-Erfurth et al., 2014) Although the introduction of anti-VEGF agents has considerable improved our treatment possibilities for the neovascular form, several major questions regarding the pathogenesis and development of AMD are still unsolved.

For clinical trials in AMD patients´ visual acuity usually tested using standardized reading charts according to Early Treatment Diabetic Retinopathy Study (ETDRS) is the most widely used clinical outcome parameter. As visual acuity is relatively simple to determine, it also serves as the clinical endpoint for pivotal studies to test new treatment modalities including anti-VEGF agents. Whereas this is well established and also accepted by the authorities as primary endpoint for drug approval studies, using visual acuity as the only measure for visual function suffers from some limitations. Most importantly, visual acuity does not reflect a person’s ability to perceive contrast, color, depth, or peripheral sight, all of which are determine to a large degree whether patients can find their way in life.

The ultimate goal of treating patients with AMD remains to improve quality of life. Although visual acuity is an important determinant of quality of life there is evidence

that central visual acuity as usually assessed in clinical routine does not necessarily correlate well with patients' perception of vision.(Richman et al., 2010) It is now understood that vision is much more complex and is only poorly reflected by standard visual tests. There is evidence that further to the optical resolution of the central retina, factors such as light sensitivity, visual field, discrimination of high spatial frequencies and color vision also are involved in the overall impression of the seeing process.(Peli, Yang, & Goldstein, 1991) Whereas these parameters can be in principle studied individually, psychophysiological tests are time consuming and not easily applicable especially in the elderly with poor vision.

Metamorphopsia is a key element of the visual disturbance associated with AMD. Several groups have investigated how visual impairment affects vision related tasks. These experiments include visual search tasks in artificial arrays (Geringswald, Baumgartner, & Pollmann, 2012; Pinkus, Poteet, & Pantle, 2013) or scene discrimination using photographs(Boucart, Moroni, Szaffarczyk, & Tran, 2013; Denniss & Astle, 2018; Head & Helton, 2012; Peyrin, Ramanoel, Roux-Sibilon, Chokron, & Hera, 2017; Thibaut, Delerue, Boucart, & Tran, 2016; Tran, Despretz, & Boucart, 2012). In the present pilot study we aimed to test a simple approach for characterizing subjective vision in AMD patients with CNV.

Photographs representing every day scenes were digitally modified to approximate patients´ description of their personal perception of distorted vision in their diseases eye. This mainly includes central scotoma, reduced color contrast sensitivity and central blurring. This approach has already been used previously to explore patient perception of vision loss in glaucoma by mimicking peripheral visual loss (Crabb, Smith, Glen, Burton, & Garway-Heath, 2013) as well as in small group of patients

with mononular AMD to reflect central visual loss as reported by patients with AMD (Denniss & Astle, 2018).

Methods

Subjects

The study was performed in adherence to the Declaration of Helsinki and the Good Clinical Practice (GCP) guidelines of the European Union. The study protocol was approved by the local Human Research Committees. After written informed consent was obtained, 20 newly diagnosed patients with CNV aged 50 years or older were included. None of the participants had had previous ant-VEGF treatment. Inclusion criteria were adequate compliance to allow for the correct completion of the questionnaire, newly diagnosed choroidal neovascularisation in one eye, confirmed subretinal fluid by optical coherence tomography not older than 3 days, confirmed choroidal neovascularisation by fluorescein angiography not older than 3 weeks, no history of late AMD in the contralateral eye, and visual acuity > 0.7 in the contralateral eye. All patients were scheduled for intravitreal anti-VEGF treatment independently of the present study. Any other eye disease that may have affect visual perception of the images as judged by the investigator was an exclusion criterion.

Protocol

The present study was performed as a multi-center trial in four private practices in Austria. A forced-choice experiment was used to assess the patient´s perception of visual loss. For this purpose, subjects were first presented the original image on the affected eye. Thereafter, modified candidate images were subsequently presented to

the contralateral eye by starting with the image with the least distortion. If the subjects were not able to make a decision after viewing the images they could also repeat this procedure. The subjects were then asked to choose one image that most closely matches the perception on the affected eye. This was subsequently repeated with 3 different images representing three every day life scenes. In addition, the patients were asked to complete a quality of life questionnaire (NEI-VF14). The images used are presented in the Appendix. The main outcome variable for this study was frequency of response to the forced choice questionnaire experiment for each image.

Presented images

Three different images representing every day life scenes were manipulated to mimic visual perception with central scotomas, reduced color perception and blurring using Adobe Phoptoshop. Image modifications were done in a central circle with four varying sizes: 0.3, 0.6, 1.2 and 2.1 mm. The images were presented to the patients in a normal reading distance of approx. 36cm with an appropriate correction for optimal vision. These central circles in the images therefore corresponded to visual angles of 0.5°, 1.0°, 2.0°, and 3.4° at the retina for the four chosen manipulations, respectively.

The three scenes were modified as follows:

1. A shopping window with different products. The shopping window was manipulated using a Gaussian blur filter with 3 increasing sizes in the center of the image, again each modified with three different increasing intensities of blurring. The central blurring effect of the Gaussian blur filter should mimic central vision loss due to blurring of the central visual field.

2. A daily street scene: The street scene was modified a) with a brightness filter to reduce brightness by 50%, 75% and 100% the latter leading to a dark area in the center of the image. Again these brightness reductions were presented in three different sizes all centered in the image. Furthermore 4 different images with a 100% desaturation of color were presented in increasing sized centered in the image. The brightness filter was design to simulate relative and absolute central scotoma, whereas the desaturation filter simulates central color perception loss.

3. A group of persons: Images were modified by a sinusoidal distortion filter centered in the image and presented in different sizes and different frequencies. As patients with CNV frequently report “wavy lines”, the sinusoidal distortion filter was designed to mimic a wavy appearance of the central image.

Images were presented in standardized size (A4 – landscape) with a controlled color profile and printed on high resolution Kodak® Photo Paper with at least 300dpi. Patients were also instructed to keep the right observation distance through the whole process.

NEI-VF14 questionnaire

NEI-VF14 is a widely used standard questionnaire to quantify quality of life in patients with disturbance.(Steinberg et al., 1994) It has shown that the VF-14 is a reliable and valid measure of visual impairment and provides information not conveyed by visual acuity or a general measure of health status.(Alonso et al., 1997)

Statistical analysis

Response from the forced-choice experiment was counted and descriptive statistics was used to describe the frequency of the responses to the particular images. Patients were divided according to visual acuity groups in those with lower visual acuity and those with higher visual acuity. Data between these groups were compared with Mann-Whitney U test.

Results

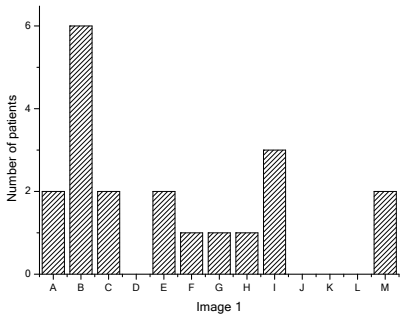
The characteristics of the study population are presented in Table 1. In 12 subjects the right eye was studied, in 8 subjects the left eye was studied. Fourteen female and 6 male subjects were studied.

Variable	Median	Range
Age (years)	79	64-93
NEI-VF14 score	84.5	50.0-97.8
Visual acuity (study eye)	0.40	0.16-1.00
Visual acuity (Contralateral eye)	0.85	0.80-1.00

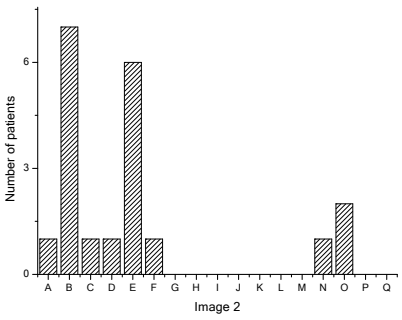
Table 1: Subjects characteristics

Figure 1 summarizes the results of image-based questionnaire. Images 1 and 2 were evaluated by all 20 patients. Image 3 was only evaluated by 18 subjects, because 2 subjects were not able to select a specific modification that matched their perception. For Image 1 most patients selected modification 1 B. For image 2 versions 2B and 2E were chosen by 7 and 6 patients, respectively. Version 3B was chosen by 8 patients.

A



B



C

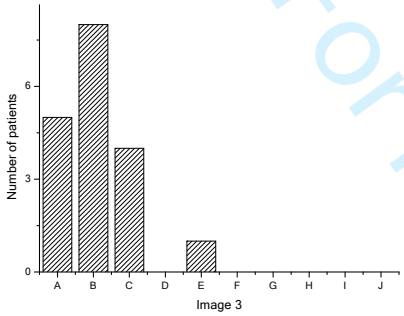


Figure 1: Frequency histograms for image questionnaire

Modifications in Images 1 and 2 most closely matched the perception on the affected eye in 9 and 10 patients, respectively. Only 1 patient chose image 3 (Figure 2).

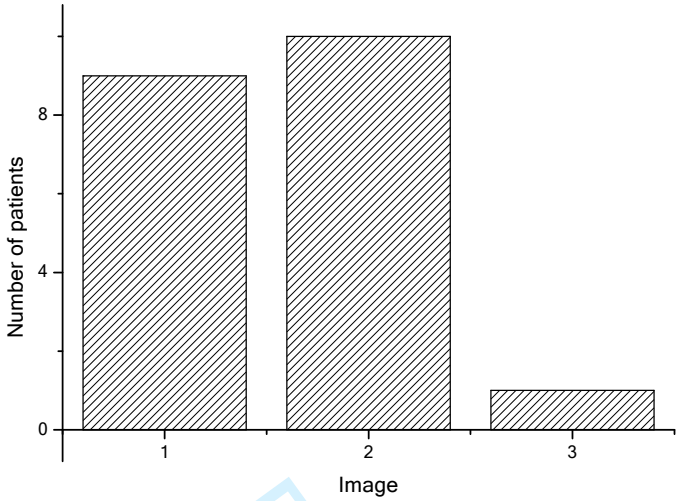


Figure 2: Image that most closely matched the perception on the affected eye.

In order to study the association between visual acuity and image questionnaire patients were grouped according to their visual acuity. Patients with lower visual acuity had a median value of 0.28 (range: 0.16-0.40, group 1), patients with better visual acuity had a median value of 0.50 (range: 0.40-1.00, group 2).

The relation between visual acuity and image questionnaire results is presented in Figure 3. In image 1 size of modification was not associated with visual acuity ($p = 0.34$), but intensity was borderline associated ($p = 0.06$). In image 2, however, the size of the modification was different between the two visual acuity groups ($p = 0.01$), whereas the intensity of modification was not related to visual acuity ($p = 1.0$). For image 3 no association was observed (data not shown).

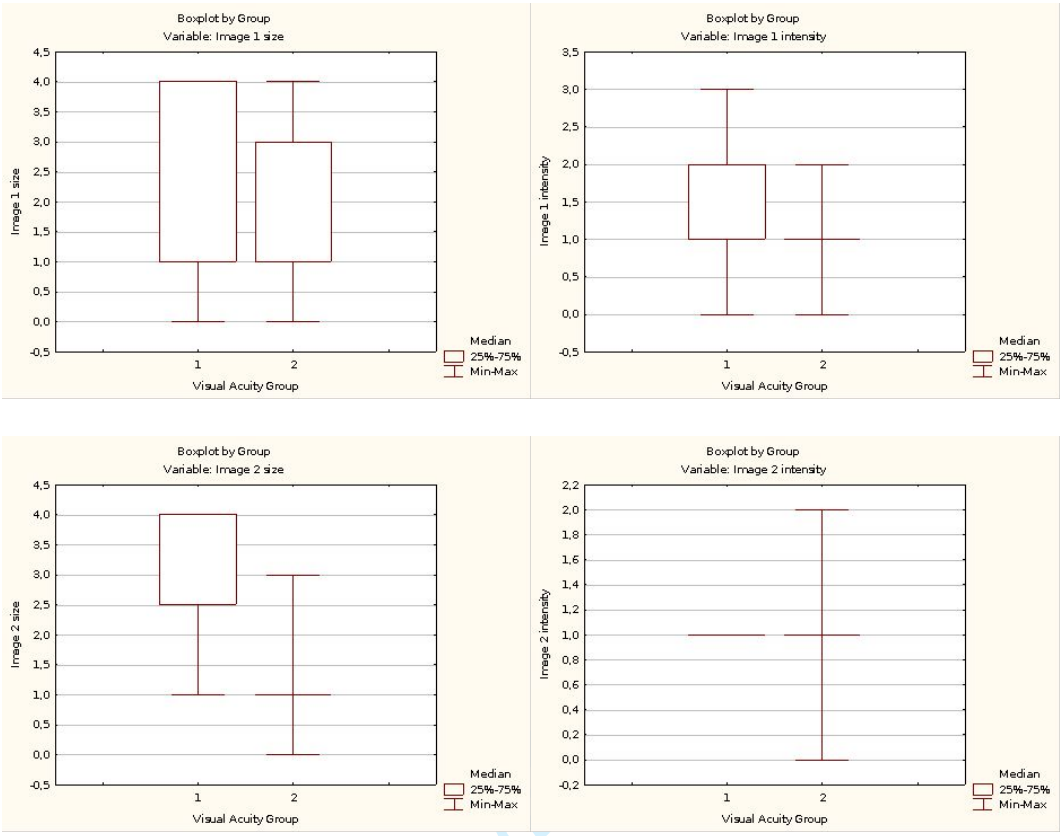


Figure 3: Relation between visual acuity and modification size and intensity for Images 1 and 2. Data for Image 3 are not shown.

Discussion

The common view on visual perception of CNV secondary to AMD is that there is a central complete scotoma, which depends on the size of the lesions. The present study indicates that this is only partially true. The majority of subjects selected either the images that were manipulated using either a Gaussian blur filter with 3 increasing sizes in the center of the image or with a brightness filter. Only one patient chose the Images that were modified by a sinusoidal distortion filter. In image 2 the modification size was clearly associated with visual acuity. Our results are compatible with a recent study in 6 patients with monocular AMD in whom image modifications required

to achieve perceptual similarity with the affected eyes included distortion, contrast reduction and blur(Denniss & Astle, 2018).

Several investigators have focused on devices to better detect metamorphopsia using different approaches(Achiron et al., 2015; Kim & Kim, 2016). Showing images as selected in the present study to patients may be an additional strategy to increase awareness of the disease and result in earlier detection of AMD-related visual disturbance. As such we chose scenes that are closely related to abilities that are lost in late AMD such as face recognition(Taylor, Hobby, Binns, & Crabb, 2016; Tejeria, Harper, Artes, & Dickinson, 2002), driving (Bronstad, Albu, Goldstein, Peli, & Bowers, 2016; Taylor et al., 2016) and shopping behavior(Lamoureux, Hassell, & Keeffe, 2004).

In the recent years there is an increased interest in patient's perception of disease. Several strategies have been tested for improving near and distance visual acuity in patients with AMD. Using specifically engineered lenses several groups were able to show that this can be achieved by cataract surgery(Hengerer, Artal, Kohnen, & Conrad-Hengerer, 2015; Potgieter & Claoue, 2014). Other approaches include specific glasses implemented with an augmented vision, which overlays enhanced edge information over the wearer's realworld view, providing contrast-improved central vision(Hwang & Peli, 2014).

In the present study we have applied different image distortions to daily life scenes in order to mimic patients´ perception of central vision. In ophthalmological textbooks and in public information material for patients, vision loss caused by AMD is often portrayed as a central black spot indicating complete central vision or blurred central

spot. Thus, in our study we have chosen to test a brightness filter to mimic the central near-absolute to absolute scotoma and a gaussian blur filter to simulate central blurring to test whether these alterations are related to the patients´ reception. Furthermore, as patients with CNV frequently describe “wavy lines”, we have generated a sinusoidal distortion filter that results in wavy appearance of the image.

These filters were were applied to three different daily life scenes. This approach was chosen because unpublished pilot experiments showed that subjects were unable to choose between 9 different distortions when only one particular scene was modified. This establishes a limitation of our approach, because the three images differ in scene properties such as content, spatial frequency, scene context and contrast, which influence perception per se(Boucart et al., 2013; Peyrin et al., 2017; Thibaut et al., 2016; Tran et al., 2012; Tran, Guyader, Guerin, Despretz, & Boucart, 2011). The present pilot study, however, identified some distortions that can be used for future experiments on a more homogenous group of images.

The present study has the character of a pilot study and several future avenues can be envisioned. On the one hand a larger study may allow for a more thorough investigation of relation between the lesions type and size and the type and size of alterations in visual perception. Larger sample size may also allow for better characterization of patients choosing images either modified with a Gaussian blur filter or with a brightness filter. The results of our study will also help us in optimizing our images in terms of color contrast or spatial frequencies for improved performance. On the other hand it may be interesting to investigate the effect of different treatment strategies on the subjective perception of everyday scenes. Indeed several studies have recently focused on quality of life related to anti-VEGF treatment(Bertelmann et

al., 2016; Bressler et al., 2016). This may facilitate patient involvement in treatment decision and communication about potential visual outcomes. Finally, it may be possible to implement changes in images by either a Gaussian blur filters with different sizes in the center of the image or with brightness filters using electronic devices. This may also allow for an easier and faster selection of the images by the patients, which is necessary to test our approach in larger patient cohorts.

In conclusion, we have observed a wide variability of subjective perception in patients with CNV secondary to AMD. The results of the study may be an important step towards the understanding of patients visual disturbance and may facilitate communication. Further studies are required to study the effects of treatment on visual perception. The present study indicates that this can be done with a subset of the images used in the present study.

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References

Achiron, A., Lagstein, O., Glick, M., Gur, Z., Bartov, E., & Burgansky-Eliash, Z. (2015). Quantifying metamorphopsia in patients with diabetic macular oedema and other macular abnormalities. *Acta Ophthalmol, 93*(8), e649-653. doi:10.1111/aos.12735

Alonso, J., Espallargues, M., Andersen, T. F., Cassard, S. D., Dunn, E., Bernth-Petersen, P., . . . Anderson, G. F. (1997). International applicability of the VF-14. An index of visual function in patients with cataracts. *Ophthalmology, 104*(5), 799-807.

Bertelmann, T., Feltgen, N., Scheffler, M., Hufenbach, U., Wiedon, A., Wilhelm, H., & Ziemssen, F. (2016). Vision-related quality of life in patients receiving intravitreal ranibizumab injections in routine clinical practice: baseline data from the German OCEAN study. *Health Qual Life Outcomes, 14*(1), 132. doi:10.1186/s12955-016-0536-1

Boucart, M., Moroni, C., Szaffarczyk, S., & Tran, T. H. (2013). Implicit processing of scene context in macular degeneration. *Invest Ophthalmol Vis Sci, 54*(3), 1950-1957. doi:10.1167/iovs.12-9680

Bressler, N. M., Varma, R., Mitchell, P., Suner, I. J., Dolan, C., Ward, J., . . . Turpcu, A. (2016). Effect of Ranibizumab on the Decision to Drive and Vision Function Relevant to Driving in Patients With Diabetic Macular Edema: Report From RESTORE, RIDE, and RISE Trials. *JAMA Ophthalmol, 134*(2), 160-166. doi:10.1001/jamaophthalmol.2015.4636

Bronstad, P. M., Albu, A., Goldstein, R., Peli, E., & Bowers, A. R. (2016). Driving with central field loss III: vehicle control. *Clin Exp Optom, 99*(5), 435-440. doi:10.1111/cxo.12432

Colijn, J. M., Buitendijk, G. H. S., Prokofyeva, E., Alves, D., Cachulo, M. L., Khawaja, A. P., . . . European Eye Epidemiology, c. (2017). Prevalence of Age-Related Macular Degeneration in Europe: The Past and the Future. *Ophthalmology, 124*(12), 1753-1763. doi:10.1016/j.ophtha.2017.05.035

Crabb, D. P., Smith, N. D., Glen, F. C., Burton, R., & Garway-Heath, D. F. (2013). How does glaucoma look?: patient perception of visual field loss. *Ophthalmology, 120*(6), 1120-1126. doi:10.1016/j.ophtha.2012.11.043

Denniss, J., & Astle, A. T. (2018). Modified images reflecting effects of age-related macular degeneration on perception of everyday scenes. *Clin Exp Optom*. doi:10.1111/cxo.12672

Geringswald, F., Baumgartner, F., & Pollmann, S. (2012). Simulated loss of foveal vision eliminates visual search advantage in repeated displays. *Front Hum Neurosci, 6*, 134. doi:10.3389/fnhum.2012.00134

Head, J., & Helton, W. S. (2012). Natural scene stimuli and lapses of sustained attention. *Conscious Cogn, 21*(4), 1617-1625. doi:10.1016/j.concog.2012.08.009

Hengerer, F. H., Artal, P., Kohnen, T., & Conrad-Hengerer, I. (2015). Initial clinical results of a new telescopic IOL implanted in patients with dry age-related macular degeneration. *J Refract Surg, 31*(3), 158-162. doi:10.3928/1081597X-20150220-03

Hwang, A. D., & Peli, E. (2014). An augmented-reality edge enhancement application for Google Glass. *Optom Vis Sci, 91*(8), 1021-1030. doi:10.1097/OPX.0000000000000326

Kim, J. W., & Kim, Y. T. (2016). Clinical application of 3D display device in ophthalmology: measurement of metamorphopsia. *Acta Ophthalmol, 94*(1), e54-58. doi:10.1111/aos.12795

Lamoureux, E. L., Hassell, J. B., & Keeffe, J. E. (2004). The determinants of participation in activities of daily living in people with impaired vision. *Am J Ophthalmol, 137*(2), 265-270. doi:10.1016/j.ajo.2003.08.003

Peli, E., Yang, J., & Goldstein, R. B. (1991). Image invariance with changes in size: the role of peripheral contrast thresholds. *J Opt Soc Am A, 8*(11), 1762-1774.

Peyrin, C., Ramanoel, S., Roux-Sibilon, A., Chokron, S., & Hera, R. (2017). Scene perception in age-related macular degeneration: Effect of spatial frequencies and contrast in residual vision. *Vision Res, 130*, 36-47. doi:10.1016/j.visres.2016.11.004

Pinkus, A. R., Poteet, M. J., & Pantle, A. J. (2013). Search performance with discrete-cell stimulus arrays: filtered naturalistic images and probabilistic markers. *Psychol Res, 77*(3), 277-302. doi:10.1007/s00426-012-0434-z

Potgieter, F. J., & Claoue, C. M. (2014). Safety and efficacy of an intraocular Fresnel prism intraocular lens in patients with advanced macular disease: initial clinical experience. *J Cataract Refract Surg, 40*(7), 1085-1091. doi:10.1016/j.jcrs.2013.10.049

Richman, J., Lorenzana, L. L., Lankaranian, D., Dugar, J., Mayer, J. R., Wizov, S. S., & Spaeth, G. L. (2010). Relationships in glaucoma patients between standard vision tests, quality of life, and ability to perform daily activities. *Ophthalmic Epidemiol, 17*(3), 144-151. doi:10.3109/09286581003734878

Schmidt-Erfurth, U., Chong, V., Loewenstein, A., Larsen, M., Souied, E., Schlingemann, R., . . . European Society of Retina, S. (2014). Guidelines for the management of neovascular age-related macular degeneration by the European Society of Retina Specialists (EURETINA). *Br J Ophthalmol, 98*(9), 1144-1167. doi:10.1136/bjophthalmol-2014-305702

Steinberg, E. P., Tielsch, J. M., Schein, O. D., Javitt, J. C., Sharkey, P., Cassard, S. D., . . . et al. (1994). The VF-14. An index of functional impairment in patients with cataract. *Arch Ophthalmol, 112*(5), 630-638.

Taylor, D. J., Hobby, A. E., Binns, A. M., & Crabb, D. P. (2016). How does age-related macular degeneration affect real-world visual ability and quality of life? A systematic review. *BMJ Open, 6*(12), e011504. doi:10.1136/bmjopen-2016-011504

Tejeria, L., Harper, R. A., Artes, P. H., & Dickinson, C. M. (2002). Face recognition in age related macular degeneration: perceived disability, measured disability, and performance with a bioptic device. *Br J Ophthalmol, 86*(9), 1019-1026.

Thibaut, M., Delerue, C., Boucart, M., & Tran, T. H. (2016). Visual exploration of objects and scenes in patients with age-related macular degeneration. *J Fr Ophtalmol, 39*(1), 82-89. doi:10.1016/j.jfo.2015.08.010

Tran, T. H., Despretz, P., & Boucart, M. (2012). Scene perception in age-related macular degeneration: the effect of contrast. *Optom Vis Sci, 89*(4), 419-425. doi:10.1097/OPX.0b013e31824c3a21

Tran, T. H., Guyader, N., Guerin, A., Despretz, P., & Boucart, M. (2011). Figure ground discrimination in age-related macular degeneration. *Invest Ophthalmol Vis Sci, 52*(3), 1655-1660. doi:10.1167/iovs.10-6003

Supplementary files

Images for the forced choice experiment