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The influence of L-opsin gene polymorphisms and neural ageing on spatio-chromatic contrast sensitivity in 20–71 year olds

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ABSTRACT

Chromatic contrast sensitivity may be a more sensitive measure of an individual's visual function than achromatic contrast sensitivity. Here, the first aim was to quantify individual- and age-related variations in chromatic contrast sensitivity to a range of spatial frequencies for stimuli along two complementary directions in color space. The second aim was to examine whether polymorphisms at specific amino acid residues of the L- and M-opsin genes (OPN1LW and OPN1MW) known to affect spectral tuning of the photoreceptors could influence spatio-chromatic contrast sensitivity. Chromatic contrast sensitivity functions were measured in 50 healthy individuals (20–71 years) employing a novel pseudo-isochromatic grating stimulus. The spatio-chromatic contrast sensitivity functions were found to be low pass for all subjects, independent of age and color vision. The results revealed a senescent decline in spatio-chromatic contrast sensitivity. There were considerable between-individual differences in sensitivity within each age decade for individuals 49 years old or younger, and age did not predict sensitivity for these age decades alone. Forty-six subjects (including a color deficient male and eight female carriers) were genotyped for L- and M-opsin genes. The Ser180Ala polymorphisms on the L-opsin gene were found to influence the subject's color discrimination and their sensitivity to spatio-chromatic patterns. The results expose the significant role of neural and genetic factors in the deterioration of visual function with increasing age.

1. Introduction

Differences in contrast are the primary signals for vision. Measurements of sensitivity to contrast are informative with regards to an individual's ability to perceive slight changes in luminance and chromaticity and gives important insight to their overall visual function. Some psychophysical studies have reported a decline in spectral sensitivity with age (Fiorentini, Porciatti, Morrone, & Burr, 1996; Knoblauch, Vital-Durand, & Barbur, 2001; Werner & Steele, 1988), with older subjects being less sensitive to spatio-chromatic contrast than younger subjects (Fiorentini et al., 1996; Knoblauch et al., 2001, for a review see reference Werner, Delahunt, and Hardy (2004). The decline in contrast sensitivity for both luminance and chromatic contrast appears to begin somewhere between 30 and 70 years of age (Fiorentini et al., 1996). The reasons for these observed senescent declines are debatable, but are commonly attributed to optical factors (Owsley, Sekuler, & Siemsen, 1983; Steen, Whitaker, Elliott, & Wild, 1994; Weale, 1988; Werner, 1982). An alternate explanation, as supported by the current work, is that the decline in sensitivity can be ascribed to neural factors (Elliott, 1987; Hardy, Delahunt, Okajima, & Werner, 2005; Higgins, Jaffe, Caruso, & deMonasterio, 1988; Sloane, Owsley, & Alvarez, 1988; Sloane, Owsley, & Jackson, 1988; Werner, Schwarz, & Paulus, 1995). An individual's chromatic sensitivity at a given age might therefore be related to the degree of loss in cone photoreceptor sensitivity.

Sensitivity, arising from a combination of signals from cone photoreceptors, is likely also to be dictated by the amino acid sequences of the (L) and (M) opsin genes (OPN1LW and OPN1MW). This is because there are considerable variations in the amino acid sequences of the L- and M-opsin genes even among subjects with normal trichromatic color vision (Neitz, Neitz, & Grishok, 1995; Winderickx, Battisti, Hibiya, Motulsky, & Deeb, 1993). Variations in the amino acid sequences of these cone opsins are responsible for spectral tuning of the photoreceptors (Neitz, Neitz, & Jacobs, 1991), and inherited red-green color vision deficiencies are due to alterations in these cone opsin genes

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(Nathans, Piantanida, Eddy, Shows, & Hogness, 1986; Vollrath, Nathans, & Davis, 1988). Polymorphisms in the L- and M-opsin genes give rise to amino acid differences that influence the spectral sensitivity of the encoded pigments. The peak sensitivity of the L- and M-pigments range from 549 to 559 nm and 530 to 533 nm respectively (Carroll, McMahon, Neitz, & Neitz, 2000). The presence of either serine (Ser) or alanine (Ala) at position 180 of the L-pigment gene has been found to be one of the most prevalent polymorphisms that results in variation of chromatic discrimination in males as measured with Rayleigh anomaloscopy (Carroll, Neitz, & Neitz, 2002; Neitz et al., 1995; Sharpe et al., 1998; Winderickx et al., 1992). Ser180 results in a green-shift in Rayleigh match-midpoints (RMMP) and a shift in peak sensitivity (~3.5 nm) of the L-cone towards longer wavelengths compared with Ala180 (Carroll et al., 2002).

Considerable variation in color vision behavior is observed among female subjects, both normal females and those that are heterozygous carriers of red-green color vision deficiencies (e.g. Crone (1959), Dees and Baraas (2014), Feig and Ropers (1978), Hill (1980), Jordan and Mollon (1993), Waaler (1927)). Females have two X-chromosomes, and the one expressed in a given cone cell is determined by X-chromosome inactivation (Lyon, 1972). Hence, both normal females and carriers may have different forms of L- and M-opsin genes on each X-chromosome (Hunt et al., 1998), and this can result in retinas that express up to five different cone pigments (two different L pigments, two different M pigments, and the S pigment; Bosten, Robinson, Jordan, & Mollon, 2005; Jordan & Mollon, 1993, 1997; Jørgensen et al., 1992). It is not unlikely that the number of expressed cone pigments and the spectral separation between these could influence sensitivity to spatio-chromatic patterns, as this would affect the photon catch by the individual's cone mosaic (Sekiguchi, Williams, & Brainard, 1993) and post-receptoral signals. Expression of more than one L- and one M-cone pigment will result in a narrower spectral separation between the expressed cones and therefore increase their spectral overlap. Alternative suggestions to whether this would affect the level of post-receptoral noise, and an increase or decrease in chromatic sensitivity, has been made following reports of differences between males and females (Murray, Parry, McKeefry, & Panorgias, 2012; Rodríguez-Carmona, Sharpe, Harlow, & Barbur, 2008).

The conundrum of chromatic sensitivity with regards to senescence and male–female differences needs to be resolved if we are to understand what causes the large variation in age-related changes in vision (Spear, 1993). Here we sought to study this from two angles combining genetics and measures of sensitivity with a novel spatio-chromatic stimulus. First, we investigated age-related variations in spatio-chromatic contrast sensitivity for stimuli along two directions in color space across a range of spatial frequencies. Second, we explored whether the deduced spectral separation between the underlying L- and M-cone photopigments influenced between-individual variation in spatio-chromatic contrast sensitivity.

2. Methods

2.1. Subjects, ocular health and color vision testing

Forty-one normal subjects (24 females and 17 males, aged 20–71 years, *Mean* = 41.0, *SD* = 17.5, Table 1), one minimally deuteranomalous male (aged 36 years), two female carriers of protan deficiencies (aged 21 and 36 years) and six female carriers of deutan deficiencies (*Mean* = 32.8, *SD* = 14.0) were included in the study. Genetic analyses of X-chromosome visual pigment genes (see Section 2.3) were carried out for 46 subjects: 16 males: *Mean* = 44.31 years, *SD* = 17.2, 30 females: *Mean* = 34.4 years, *SD* = 14.1), including the color deficient male and the eight female carriers (see also Table 2). Four normal subjects were not available to give a biological sample.

The subjects were healthy with no known ocular abnormalities. Fundus photos of the central 45° (Topcon TRC-NW6S), and spectral domain optical coherence tomography with 30° scan-width with 2 and 49 B-scans (100 and 20 frames, respectively), 512 A-scans/B-scan (SD-OCT, Spectralis™ SD-OCT system, Heidelberg Engineering, Heidelberg, Germany) were performed on each subject and found to be normal and free of eye disease. The density and opacities of the eye lens was evaluated with a slit lamp microscope and graded with The Lens Opacities Classification System III (LOCS III), and were required to be no greater than grade 2 (Chylack et al., 1993). None of the subjects had undergone cataract operation.

The subjects were corrected to best logMAR visual acuity, used optimal spectacle or contact lens correction for the distance tested and viewed the stimulus monocularly using their preferred eye with natural pupils. Their statuses of either normal or carrier were confirmed by family history and genetic analysis of the genes encoding the L- and M-cone pigments (for more details see Section 2.2). Color vision was assessed with several standard color vision tests, including Ishihara (24 pl. ed., Kanehara trading INC, Tokyo, Japan), Hardy–Rand–Rittler fourth edition (HRR, Richmond Products, Albuquerque, NM; Bailey, Neitz, Tait, & Neitz, 2004; Cole, Lian, & Lakkis, 2006), Rayleigh anomaloscopy (HMC Oculus Anomaloscope MR, Typ 47700, Oculus Optikgeräte GmbH, Germany) and Medmont C-100 (Medmont Pty Ltd, Vermont, Australia). Each test was administered and performed according to its accompanying guidelines. The HRR and Ishihara plates were administered in an otherwise darkened room with the 'True Daylight Illuminator with Easel' (color temperature 6280 K, model number 1339R, Richmond Products, Albuquerque, NM). The level of illumination was measured at the surface of the test plates with a digital lux meter (Hagner Model EC1, Hagner AB, Solna, Sweden), and averaged about 900 lux. Written test procedures were strictly followed. A single operator (author EWD, a qualified optometrist) collected all the data.

Informed consent was obtained from all subjects after the nature of the study and possible complications were explained both verbally and in writing. The research was approved by the Regional Committee for Medical Research Ethics for the Southern Norway Regional Health Authority and was conducted in accordance with the principles embodied in the Declaration of Helsinki (Code of Ethics of the World Medical Association).

2.2. Spatio-chromatic contrast sensitivity

Spatio-chromatic contrast sensitivity was measured in all subjects, employing a novel pseudo-isochromatic grating stimulus along two complementary directions in color space. The stimulus (Fig. 1) was a chromatic sinusoid grating with a pseudo-isochromatic design that consisted of an array of spatially discrete round spots of varying size and luminance. The principle of the design is similar to that used in pseudo-isochromatic plates (Regan, Reffin, & Mollon, 1994; Stilling, 1918).

The spots that made up the background had a single chromaticity. The spots that made up the grating had a chromaticity determined by the mean color of the region of the grating covered by each spot.

A grating is produced by the addition of two sine waves (L_1, L_2) where luminance and contrast of both of them may be changed in an interrelated manner. L_0 is the mean luminance of the resultant grating. Spatial luminance distribution is described as a function of phase φ, and luminance and contrast ratios r_1 and r_2 respectively: $L_1(r_1, r_2) = r_1 \times L_0 \times (1 \pm r_2) \times m \times \cos\varphi$ and $L_2(r_1, r_2) = (1 - r_1) \times L_0 \times (1 \pm r_2) \times m \times \cos\varphi$.