Alterations of the Visual Perception in Advanced Age-Related Macular Degeneration

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Abstract: Age-related macular degeneration is a retinal disease causing the progressive loss of macular vision, typically in people over 60 years of age. It will become a major public health problem in the next years as the population of aged people is expected to increase. In the advanced stage of the disease, development of the central retinal lesion provokes a central scotoma in the visual field. Consequently, at this stage, patients only rely on the use of peripheral vision to achieve visual tasks. The exclusive use of the peripheral retina itself modifies visual perception by reducing visual acuity and contrast sensitivity, and by increasing crowding effects, i.e. contour interaction. Visual perception is further modified by mechanisms of cortical plasticity taking place following the development of the retinal lesion. These mechanisms induce a variety of perceptual changes including filling-in, altered perception of space and Charles Bonnet syndrome. While some modifications of visual perception, such as reduction of visual acuity and contrast sensitivity are well known, occurrence of other phenomena like crowding effect and Charles Bonnet syndrome is generally underestimated. The aim of this review is to discuss the major factors modifying visual perception in patients with advanced age-related macular degeneration and to relate these phenomena to patients' visual difficulties in everyday life.

Keywords: visual perception, age-related macular degeneration, central scotoma, eccentric viewing

Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is a retinal disease causing the progressive loss of macular vision, typically in people over 60 years of age. AMD is the primary cause of visual impairment in industrialised countries and the third cause worldwide (Resnikoff et al. 2004). The prevalence of AMD among persons older than 65 years is at least 8% and further increases with age (Bonastre et al. 2002; Smith et al. 2001). According to the World Health Organisation, the prevalence of AMD-induced legal blindness, i.e. visual acuity under 0.1 and not improvable or visual field extent less than 20 degrees, is 8.7%. AMD is consequently becoming an important public health problem since the population of aged people is expected to increase by more than 50% in the next twenty years (Klein et al. 2005). Therefore, understanding the functional adaptation mechanisms following the development of the central macular lesion is a key point in research and clinical practice for patient's psychosocial adaptation and for the set up of adapted rehabilitation procedures.

One of the earliest symptoms of AMD is the occurrence of metamorphopsia, characterised by a distorted perception due to the deformation of the retina. For example, patients may perceive a pillar as wavy. In the advanced stage of the disease, visual perception is further affected by the development of a macular lesion and by the consecutive exclusive use of the peripheral retina. Age-related macular degeneration, in its advanced stage, can be either non-neovascular (dry, atrophic, or non-exudative) or neovascular (wet or exudative). Although non-vascular and vascular AMD are characterised by different symptoms (Jager 2008), they both result in the development of a dense scotoma in the centre of the visual field (Fig. 1). Such a scotoma impairs visual performance in multiple tasks, such as face recognition (Peli et al. 1991) and space perception (Turano and Schuchard, 1991), the latter likely contributing to the feeling of insecurity that AMD patients might have when they walk. Additionally,

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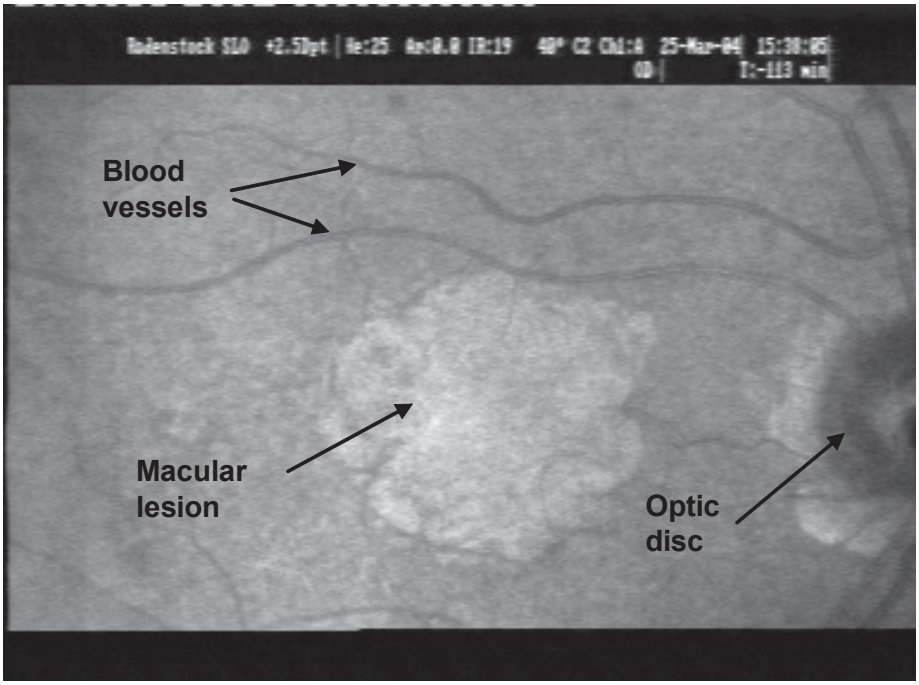

Figure 1. Macular lesion. The macular area following the development of a macular lesion due to neo-vascular age-related macular degeneration, as seen in scanning laser ophthalmoscopy. The macular lesion causes a blind area at the centre of the visual field, referred to as a central scotoma. Please note that the position of features in the scanning laser ophthalmoscopy pictures are up-side-down inverted compared to their respective positions in the visual field.

the presence of the scotoma especially affects instrumental daily living activities such as reading and writing (Cummings et al. 1985; Legge et al. 1985b; Fletcher et al. 1999; Bullimore and Bailey, 1995; Faye, 1984; Whittaker and Lovie-Kitchin, 1993). Visual functions such as contrast sensitivity (Mitra, 1985; Schuchard, 1992), stereoscopic depth perception (Raasch, 1991) and fixation stability (Schuchard, 2000) are also highly affected.

Eccentric Fixation and Preferred Retinal Locus

Adaptation of a preferred retinal locus

Originally, the oculomotor system has developed to project images of the visual field onto the fovea, i.e. the most central part of the macula. Following the development of a central scotoma, this oculomotor mechanism is no longer efficient and needs to readapt. In 1962, von Noorden and Mackensen showed that patients with central scotomas generally developed, with time and practice, a preferred retinal area for fixation on a spared part of the retina outside the lesion, and consequently achieved eccentric fixation. Functional use of such retinal areas is nowadays widely accepted and these areas are referred to as preferred retinal loci (PRL) (Timberlake et al. 1987; White and Bedell, 1990; Schuchard and Raasch, 1992; Cummings et al. 1985; Timberlake et al. 1986; Whittaker et al. 1988) (Fig. 2). Eccentric fixation naturally and reliably occurs when the foveal area in both eyes is no longer functioning; although the selection and use of a PRL depends on the age and individual capability (Von Noorden and Mackensen, 1962; Dalgleish and Naylor, 1963; Cummings et al. 1985; Timberlake et al. 1986; Timberlake et al. 1987; Whittaker et al. 1988; White and Bedell, 1990). In fact, 84% of affected eyes develop an established PRL (Schuchard and Fletcher, 1994) and, in case of stable lesion of the central retina, that PRL becomes the new reference point for the oculomotor system replacing the altered fovea (White and Bedell, 1990; Trauzettel-Klosinski and Tornow, 1996). However, the PRL does not provide a spatial visual discrimination as detailed as the fovea and the fixation remains very instable which complicates the performance of low vision rehabilitation procedures.

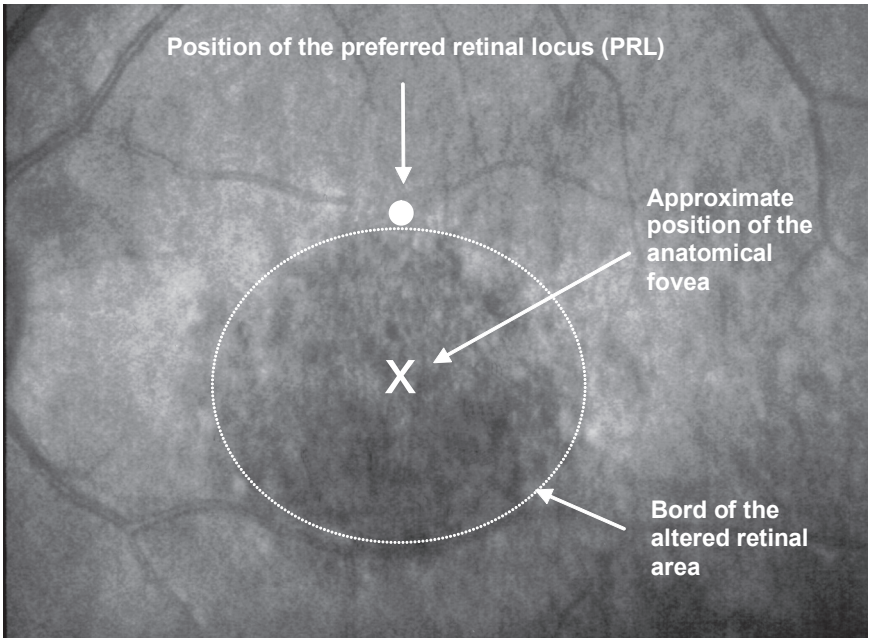

Figure 2. Eccentric fixation and preferred retinal locus (PRL). Eye fundus image as obtained with scanning laser ophthalmoscopy. Following the development of a central macular lesion the fovea can no longer be used to scrutinize objects and as reference point for the oculomotor system. Over time, the affected subject get used to eccentric viewing by fixating with the preferred retinal locus (PRL) positioned next to the altered retinal area. The PRL becomes progressively a new retinomotor reference point. The most frequent position of the PRL, over the retinal lesion, is shown in the figure. It should be remembered that images obtained with scanning laser ophthalmoscopy are displayed up side down inverted compared to positions in the visual field. Thus in this figure, the PRL shown over the retinal region is in fact located under the scotoma in the visual field.

In principle, a PRL can be selected anywhere around the lesion. Yet, the location of the PRL relative to the scotoma is critical for accomplishing tasks such as reading, (Cummings et al. 1985; Timberlake et al. 1986; Timberlake et al. 1987; Legge et al. 1992; Schuchard et al. 1999), face recognition (Peli et al. 1991), visual search (Schuchard et al. 1999) and space perception (Turano and Schuchard, 1991) since it also determines the part of the visual field that will be obstructed by the scotoma. A variety of factors might influence the selection of PRL position, including visual acuity, obstructive characteristics of the scotoma in the visual field, size of the visual span—i.e. the amount of information which can be perceived in a single fixation, proximity to the original fovea, interocular correspondence of the altered areas and variations of sustained attention at different positions of the visual field (Mackeben, 1996; Mackeben, 1999; Schuchard and Fletcher, 1994; Altpeter et al. 2000). Probably, the region selected as PRL will be the one presenting the most adapted combination, or compromise, between these factors. Several clinical studies reported that the PRL is most often placed under (from 39% to 93% of the cases) (Fletcher and Schuchard, 1997; Somani and Markowitz, 2004; Trauzettel-Klosinski and Tornow, 1996; Guez et al. 1993; Acosta et al. 1991; Rohrschneider et al. 1997), or to the left of the altered area in the visual field (from 33% to 63%) (Fletcher and Schuchard, 1997; Sunness et al. 1996; Acosta et al. 1991; Guez et al. 1993; Rohrschneider et al. 1997).

Multiple preferred retinal loci

The variability of adaptation to a central scotoma is further increased by the possibility of using multiple PRL to accomplish different visual tasks. It has indeed been reported that some patients with AMD could adapt their eye movement behaviour and used multiple PRL in combination, each of them having a specific function. The switch from one oculomotor reference point, the fovea, to several PRL suggests that eye movement control is capable of considerable plasticity (Whittaker et al. 1988; Duret et al. 1999a; Safran et al. 1999a). The development of multiple PRL has been reported during different visual task. The combined use of two PRL, one located within the scotomatous area and the second one located on an eccentric location has been observed to view

images of restricted size (PRL within the scotoma) or of large size (eccentric PRL) (Guez et al. 1993; Trauzettel-Klosinski and Tornow, 1996; Sunness et al. 1995). Furthermore, alternate use of different PRL has been reported in specific illumination conditions (Lei and Schuchard, 1997), can be influenced by distance vision (Crossland et al. 2004a) and induced by the reading process (Duret et al. 1999a; Safran et al. 1999a; Deruaz et al. 2002). Finally it has recently been suggested that multiple PRL are more likely to develop in patients having suffered recent vision loss in the tested eye (Crossland et al. 2004b).

Alternate use of PRL can interfere with perimetry and other test performance. For example, in low vision rehabilitation, the determination of gaze directions using simple methods, such as asking the subject to evaluate the quality of images presented at different positions in the visual field, allows an easy assessment of a single PRL position (own unpublished data). However, using such methods, the presence and the position of the multiples PRL can be difficult to determine.

Many questions concerning eccentric fixation remain unsolved, including how and why a PRL develops in a particular area of the retina, why some patients develop multiple PRL, as well as why some patients can much better adapt to their deficit than others.

Binocular viewing and AMD

As previously mentioned, binocular viewing may be crucial in the selection process of PRL. Indeed, as AMD doesn't affect both eyes equally, the different input from each eye affects binocular function (Quillen, 2001). However, very few studies addressed the question of binocular viewing in advanced AMD, probably because this particular issue is difficult to study. Indeed, most studies addressing the question of PRL location and use were conducted with scanning laser ophthalmoscopy, a valuable technique allowing direct and real time view of both the retina and the superimposed stimulus, but which is restricted to monocular examinations. At the moment, no technique allow the viewing of both retinas and stimuli simultaneously. This highly restrains research on binocular vision in subjects affected by AMD because it renders impossible to objectively determine where the patient is looking while performing a task. Only subjective assessments can be made. One of the few studies addressing the question of PRL under binocular conditions was conducted on eye movements analysis (Kabanarou, 2006). Results showed a change in gaze position during binocular viewing as compared with monocular viewing (Kabanarou, 2006).

In normally sighted individuals, binocular visual performance is known to be better than either of the two monocular performances. This phenomenon is called binocular summation (Blake and Fox, 1973). But a difference in inputs from each eye might also conduct to binocular inhibition (Pardhan et al. 1990; Tarita-Nistor et al. 2006a and b). In AMD the different input from each eye might lead either to binocular summation or to binocular inhibition depending on the considered function, for example visual acuity or contrast sensitivity.

Finally, even if the inputs from both eyes are similar, they do not equally contribute to visual perception. In fact, one has generally a tendency to prefer or to stronger process visual input from one eye to the other. This is called eye dominance. Determining eye dominance can be achieved by the following simple test. First, one should fixate a small target located about 2–3 meters away with both eyes through a small opening. When the opening is small enough to barely allow seeing the target, one should close one eye, then the other. The non-dominant eye will not see the target when the dominant eye is closed.

Eye dominance might play an important role in the adaptation of binocular perception to a central scotoma. In fact the dominant eye is not always the better eye. It consequently leads to two possible situations in low vision rehabilitation: either the dominant eye is the better or the worse seeing eye. If the dominant eye is the worse seeing eye it might render the prescription of magnifiers or other low vision rehabilitation procedures more complex. However, the exact influence of eye dominance on binocular function and in rehabilitation procedures in patients with AMD still needs to be scientifically determined.

Altered Visual Perception Due to the Loss of Central Retina and the Exclusive Use of the Peripheral Retina

Despite all adaptations, fixation with one or several PRL remains very different from foveal fixation because of the exclusive use of the peripheral

retina and of the modified visual perception due to retinal and cortical plasticity.

Visual acuity

The maximum level of visual acuity that can be achieved at different eccentricities directly depends on the organisation of the retinal cells. The photoreceptors are indeed organised in a mosaic of two types of cells, the cones and the rods, both having different properties for signal transduction. The foveal area is exclusively constituted of cones. A good visual acuity is supported by a stacked arrangement of very small cones in the fovea. The farther from the fovea, the larger the cones and the wider the space between them, which is filled with rods. Consequently visual acuity decreases with distance from the fovea. The variation of visual acuity is additionally asymmetrical along the different meridians (Wertheim, 1894; Millodot and Lamont, 1974; Timberlake et al. 1987).

In patients with AMD, despite central vision loss, unequal scotomas in the two eyes and high interocular acuity differences, the ability of the visual system to combine the inputs from the two eyes is preserved (Tarita-Nistor, 2006a). Binocular visual acuity is therefore as good as, or better than, monocular visual acuity obtained with the better eye. One should however keep in mind that in those patients visual acuity alone is a good predictor neither of the difficulties in daily living activities, nor of the extend of the psychosocial problems that they can meet (Bäckmann, 2000). The value of visual acuity is generally overestimated on the clinical side. It has in low-vision rehabilitation practice an important but not central role.

Contrast sensitivity

Contrast sensitivity refers to the ability to distinguish shades of grey. People having a reduced contrast sensitivity have difficulties to see a light grey stimulus on a white background, for example. Patients with AMD often have reduced sensitivity to contrast, which complicates the achievement of several everyday tasks, such as reading. In order to read the daily newspapers patients with AMD will need a magnifier to correct for their reduced visual acuity. However, even when using a magnifier some patients will still not be able to read the newspaper because they will not clearly distinguish the text from the background. Indeed daily newspapers are generally printed in a relative dark shade of grey on a light grey background.

Visual acuity and contrast threshold are co-dependent. Indeed the visual acuity that can be obtained on a particular type of stimuli depends on the contrast of the stimuli. Like visual acuity, contrast sensitivity decreases with distance from the fovea for all spatial frequencies. The decrease is, however, more rapid along the vertical meridian than along the horizontal meridian (Rijsdijk et al. 1980; Pointer and Hess, 1989). Similarly to visual acuity, different contrast sensitivities can be measured at the same distance from the fovea but in different directions. But unlike visual acuity, contrast summation in the periphery occurs only when monocular sensitivities are equivalent (Pardhan and Whittaker, 2000). A difference in contrast sensitivity between both eyes results in a decreased binocular contrast sensitivity. As a consequence, in about 50% of AMD patients contrast sensitivity is further reduced under binocular testing conditions (Faubert and Overbury, 2000; Valberg and Fosse, 2002). The binocular inhibition phenomenon may complicate the adaptation of optical devices and low vision rehabilitation procedure for patients with AMD.

Finally, unlike visual acuity, contrast sensitivity threshold in patients with AMD correlates with the difficulties to achieve activities of the daily living and with psychosocial adaptation (unpublished data). The measurement of contrast sensitivity should thus play an important role in clinical practice as well as for all low vision rehabilitation oriented on daily living activities.

Crowding

Crowding is a perceptual phenomenon also referred to as contour or spatial interaction. It results in a better acuity for a single isolated letter than for words in which letters are in close proximity. The phenomenon plays a very important role for patients with advanced AMD, since it can be a major impediment to reading. As a consequence of crowding, letters in a word overlap and reading is less accurate. Thus, for example, instead of a double "n" patients with AMD may perceive the letter "m".

Crowding varies with eccentricity (Bouma, 1970; Wolford and Chambers, 1984; Strasburger et al. 1991; Toet and Levi, 1992; Kooi et al. 1994; Levi et al. 2002; Chung et al. 2001). It occurs at an imperceptible degree in central vision and is amplified in eccentric vision (Leat et al. 1999). The contour interaction zone increases with eccentricity at a much greater rate than visual acuity decreases, and thus crowding in peripheral vision does not scale with target size. Indeed, if we consider the eccentric location at which foveal threshold is doubled, it corresponds to an area 1–2 ° away from the fovea for visual acuity but only 0.1–0.2 ° for crowding (Latham and Whitaker, 1996). Therefore, increasing letter size with magnification devices might solve visual acuity problems but does not necessarily suppress crowding effects. Hence due to overlapping letters in words reading remains often suboptimal.

Neuronal Plasticity in AMD

Retinal degeneration is often related to loss of the sensory retina, leaving the neural retina deafferented. The neural retina reacts to this process by remodelling through mechanisms involving synaptogenesis and structural changes, as shown in several experimental studies (Wong, 1997; Banin et al. 1999; Peng et al. 2000; Strettoi and Pignatelli, 2000; Aleman et al. 2001; Strettoi et al. 2002; Strettoi et al. 2003; Marc et al. 2003; Ren et al. 2001; Jones et al. 2003). Neuronal reorganisation includes rapid and long-term changes. Rapid changes might reflect unmasking of existing connections, while long term changes reflect mechanisms involving synaptogenesis (Gilbert and Wiesel, 1992; Darian-Smith and Gilbert, 1994). At the cortical level, retinal lesions result in a shrinkage of the representation of the lesion and in an expansion of the representation of the retinal parts surrounding the lesion (Gilbert et al. 1990; Kaas et al. 1990; Chino et al. 1992; Heinen and Skavenski, 1991; Gilbert and Wiesel, 1992; Darian-Smith and Gilbert, 1994; Obata et al. 1999). Shifts in topography of retinal representations, as well as increases of receptive fields' size, are accordingly detected as signs of lesion-induced neuronal reorganisation after retinal and cortical lesions (Eysel et al. 1999; Gilbert and Wiesel, 1992; Kaas et al. 1990; Dreher et al. 2001). The immediate changes following retinal lesion may represent the neural substrate of perceptual phenomena such as filling-in (Yarbus, 1957; Crane and Piantanida, 1983; Ramachandran and Gregory, 1991; Paradiso and Nakayama, 1991; Gilbert and Wiesel, 1992; Pettet and Gilbert, 1992).

Altered Visual Perception Due to Cortical Plasticity

Perceptual filling-in

During monocular viewing of a scene, we do not perceive the deficits in the visual field, or scotoma, caused by the physiological blind spot or by the photoreceptors overlaid by blood vessels (Walls, 1954; Ramachandran and Gregory, 1991; Ramachandran, 1992; Safran et al. 1995) because they are invaded by surrounding information. This completion phenomenon is called perceptual filling-in. Filling-in is an important mechanism occurring after focal visual deafferentation. It leads to the perception of visual stimuli in part of the visual field where there is no visual input (Safran and Landis, 1996a; Safran and Landis, 1999). Perceptual completion of scotomas is likely to involve cortical reorganisation at multiple levels (Ramachandran and Gregory, 1991; Zur and Ullman, 2003) and is probably due to the expansion and shift of receptive fields in cells of the visual cortex (De Weerd et al. 1995; Pettet and Gilbert, 1992; Cohen et al. 2003). Modifications of receptive fields would conduct to the gradual covering of the perceptual hole (De Weerd et al. 1995). The lost function is actually not restored but there is a completion of the gap in perception (Safran and Landis, 1996a).

Perceptual filling-in has been reported in patients with acquired scotomas from retinal and cortical disorders (de Weerd et al. 1998; Safran and Landis, 1999; Sergent, 1998; Cohen et al. 2003; Gassel and Williams, 1963a and b; Gerrits and Timmerman, 1969; Ramachandran, 1992). The extent of perceptual filling-in might depend on the position and the size of the scotoma. In patients with advanced AMD, filling-in of the scotoma is often incomplete and, in case of bilateral lesions, the less severely affected eye is usually the one experiencing the most important perceptual filling-in phenomenon at the scotoma level (Cohen et al. 2003).

A practical consequence of the perceptual filling-in is the unawareness of visual field defects and, as a result, a low sensitivity to visual field

evaluation techniques based on definition of the scotoma by the patient, such as the Amsler grid (Schuchard, 1993; Achard et al. 1995; Safran and Landis, 1998). Indeed, as Cohen and colleagues (2003) showed, 31% of patients with advanced AMD underestimated the size of their scotoma when compared to the size obtained with microperimetry. As emphasised in clinical studies, low vision rehabilitation of patients with AMD might be complicated by the unawareness or the underestimation of the visual disorder (Safran and Landis, 1999). The dissociation between the actual and perceived defect, when understood, can help patients to cope with their visual defect (Safran et al. 1999b). To this aim, Safran and Landis (1996b) devised a simple clinical test. They suggested to firstly plot the subjective appearance of the defect using the Amsler grid. The patient is asked to fixate the centre of the grid and to draw the area which appears to him as missing or in which the lines are distorted, i.e. to delineate the subjectively perceived visual field defect. Secondly, the examiner determines on the same Amsler grid the objective visual field defect using a small tangent screen-type stimulus, for example a cotton swab. By having both the subjective and the objective delineation of the defects on the same grid, the examiner can explain to patients the extent of the perceptual filling-in phenomenon.

Altered perception of space

The presence of a scotoma in the visual field reduces the capacity of determining relative positions of objects in space (Kapadia et al. 1994). In a clinical condition it results in a distorted visual perception. Kapadia et al. (1994) demonstrated that normally sighted participants under conditions of a simulated scotoma tend to misplace objects with a strong bias towards the interior of the scotoma. The shift was attributed to a false evaluation of positions due to receptive fields' expansion within the artificial scotoma. Such a shift has also been reported in patients (Safran and Landis, 1996a). The consequences of this altered perception of space can be important and interfere, for example, with reading. During the reading of a word, letters located on either side of the gap in perception, created by the scotoma, may be perceived as adjacent (Safran and Landis, 1996a; Legge et al. 1997). Consequently patients may be unaware of their perceptual gap and misread a word. For example, a patient with AMD must read the word "university". His scotoma's width equals five letters of the presented word. If the patient had a space preserving representation of the stimulus, he would see the word as "uni-----ty", where the missing letters represent the spatial extent of the scotoma. However, if the perceptual space is sewn shut across the scotoma, the word representation could be "unity" (Safran and Landis, 1996a).

Patients' altered perception of space is also likely to contribute to their feeling of insecurity while walking.

Charles Bonnet syndrome

In addition to an altered visual perception, patients suffering from AMD often experience visual hallucinations. The occurrence of these hallucinations is yet underrated in clinical practice. A reason for this underestimation is that patients with AMD generally report visual hallucinations only when they are specifically asked about, but rarely spontaneously (Mitchell and Bradley, 2004). In fact, the patient's ignorance about the existence of this visual phenomenon may worry him about his mental well-being.

Visual hallucinations following a marked visual acuity loss, in the absence of cognitive impairment, are referred to as Charles Bonnet syndrome. AMD is the most common condition leading to Charles Bonnet syndrome (Jacob et al. 2004). About 15% of the AMD patients experience such visual hallucinations (Teunisse, 1995; Teunisse, 1996; Cohen et al. 2000; Abott et al. 2007). A displacement of the macula, such as macular translocation, or a PDT induced retinal traction, may be sufficient to trigger the occurrence of this syndrome in patients suffering from the neo-vascular form of AMD (Cohen et al. 2003; Cohen et al. 2000; Au Eong et al. 2001).

Charles Bonnet syndrome is characterised by episodes of simple or complex visual hallucinations. Simple hallucinations include photopsia (flashes or lights), lines or patterns, while the complex hallucinations refer to well formed and relatively stereotyped images, such as animals and figures in bright colours and dramatic settings (Jacob et al. 2004). The origin of these visual hallucinations remains unclear but they could be due to a release phenomenon resulting from sensory deprivation (Cogan, 1973). Alternately, it could be induced by

a mechanism of filling-in at a high visual processing level (Whatham et al. 2003).

Conclusion

We have reviewed the major causes of modification of the visual perception in patients with advanced AMD. While some of these factors, such as visual acuity, are well-known, others, such as visual hallucinations, are still underestimated in clinical practice. We have also pointed out that the threshold values of some well-known factors, such as visual acuity and contrast acuity, differed when they are measured under binocular and monocular conditions. We have highlighted that making the patient aware of the difference between the objective and perceived visual field defects might improve the efficiency of low vision rehabilitation. Finally we have emphasized that informing patients about the common occurrence of visual phenomena after the development of central macular lesions, such as visual hallucinations, may help the patient to better cope with his visual deficit as well as with the psychosocial consequence of AMD.

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Disclosure

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