THE DEVELOPMENT OF VIEWING STRATEGIES IN PATIENTS WITH MACULAR DISEASE

Michael Dominique Crossland

Institute of Ophthalmology, University College London

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Abstract

**Background:** This thesis describes the results of the first longitudinal study of visual behaviour in patients with newly developed macular disease (MD). The study is of a natural history, case series design. **Methods:** Twenty patients with age-related macular disease and five with juvenile forms of MD were recruited. All patients had developed scotomas in their second affected eye within the previous two weeks. Patients were assessed five times over the next twelve months. In addition to clinical tests, fixation behaviour was assessed using a scanning laser ophthalmoscope, eye movements were measured using an infra-red eyetracker and reading speed was recorded. Multivariate statistical techniques were applied to determine which factors limit reading speed and which variables lead to a change in reading speed. **Results:** All 25 patients developed a preferred retinal locus (PRL) within six months. Sixteen patients made an adaptation whereby they were unaware of using the PRL. By the end of the study, fifteen patients (60%) repeatedly made eye movements which displayed the characteristics of non-foveating saccades. Saccade efficiency reached normal levels in eight patients (32%). Over the course of the study, reading speed improved in four patients (16%), deteriorated in 7 patients (28%) and remained constant in the remaining 14 patients. Changes in reading speed were due to changes in fixation stability, non-awareness of using the PRL and developing a strategy of repeatedly using the same number of PRLs. The likelihood of a change in reading speed could not be predicted by disease type, visual acuity or scotoma size. **Conclusions:** It was not possible to predict which patients’ reading speed will change from the measures used in this study. The conclusions of this thesis have implications for the counselling of patients with macular disease and the development of training programs for patients with this common, debilitating condition.
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Chapter 1: Introduction

Visual function in patients with macular disease is notoriously difficult to predict; two patients with apparently identical clinical features can exhibit very different levels of impairment. Clinicians in low vision clinics frequently ascribe these differences to adaptive strategies adopted by patients. This thesis investigates the development of these strategies in patients with newly developed macular disease (MD), with particular reference to the development of the preferred retinal locus (PRL) and eye movements made to this PRL. The benefit of each strategy will be assessed, with reading speed being the major outcome measure. The findings of this thesis will be beneficial to those involved in the rehabilitation or counselling of patients with macular disease, as well as to the development and implementation of training programs for patients with MD.

By way of introduction, this chapter will first describe the healthy macula and the different types of macular disease. Function and rehabilitation in macular disease will then be discussed, including the concept of the preferred retinal locus. An introduction to eye movements and reading with and without foveal function will follow. Finally, the project's hypotheses will be repeated.

1.1 The human macula

1.1.1 Anatomy
The definition of the macula varies between clinicians and anatomists (Lovie-Kitchin & Bowman, 1985). Biologists define the macular region as being the part of the posterior retina containing two or more layers of ganglion cells and xanthophyllic pigment (Gass, 1987).

The central 1.5mm of this macular region appears darker than the surrounding retina on ophthalmoscopy. This area is known as the fovea centralis by anatomists and is what clinicians refer to as the macula. It subtends around 5 degrees of visual field.

The foveola is the concave floor of the fovea. Typically measuring around 0.35mm
across it is notable for a complete absence of rod photoreceptors and ganglion cells. Cones in this area are the smallest (diameter 1.5 μm) and the most densely packed of the retina (ca. 199,000 cones/mm²) (Cohen, 1992).

1.1.2 Function
The macula demonstrates the best visual acuity of the retina and there is a rapid decline in visual acuity (VA) with increasing distance from the macular centre (figure 1.1; Weymouth et al., 1928; Ludvigh, 1941; Virsu et al., 1987; Anderson et al., 1991; Latham & Whitaker, 1996b). Similar effects are observed for reading speed (Turano & Rubin, 1988; Latham & Whitaker, 1996a), contrast sensitivity (Rovamo et al., 1978) and colour vision (Stromeyer et al., 1992).

![Figure 1.1. Variation of achromatic spatial resolution with eccentricity across the human retina. (After Anderson et al., 1991).](image)

1.1.3 Definitions
The definitions used in this thesis have been based on those used by Gass (1987), viz:

**Macula lutea**: The central part of the retina which contains xanthophyll pigment and two or more layers of ganglion cells.

**Fovea**: The depression in the inner retinal surface in the centre of the fovea.

**Foveola**: The central floor of the fovea.
1.2 Macular disease

Macular disease (MD) is a term which can be applied to a group of conditions, all of which can lead to the development of a relative or absolute scotoma within the area of visual field corresponding to the foveal region.

The World Health Organisation estimates that 8 million people are severely visually impaired as a result of MD (World Health Organisation, 1997) and MD accounts for half of all blind registration in the UK (Bird, 1996; Evans et al., 1996). Results of a recent cross sectional study indicate that 3.7% of people aged over 74, and nearly 15% of those over 90 years of age suffer visual impairment due to age-related macular disease (AMD) (Evans et al., 2004). As the number of people aged over 65 is expected to grow by 30% by 2021 (Shaw, 1998), the number of individuals with AMD will increase. Further, the incidence of AMD appears to be increasing at a faster rate than can be explained solely by ageing of the population (Evans & Wormald, 1996).

Pictorial representations of ARM and AMD can be found in figure 1.2.

1.2.1 Age-related maculopathy and age-related macular disease

1.2.1.1 Age-related maculopathy (ARM)

ARM is a term given to any age-related macular changes which do not occur as a consequence of another disorder or process, such as trauma or inflammation. In 1995 the International ARM epidemiological study group (IAESG) produced a standardised classification and grading system for ARM and AMD. This definition requires the presence of either soft drusen, or hyperpigmentation of the outer retina or choroid associated with soft drusen, or hypopigmentation of the retinal pigment epithelium (RPE) in order for a diagnosis of ARM to be made.

Soft drusen are observable on funduscopy as large yellow lesions with indistinct edges. They are caused by a build up of lipid deposits between the inner collagenous layer of Bruch’s membrane and the basal lamina of the retinal pigment epithelium (Pauleikhoff et al., 2003a).
1.2.1.2 Geographic atrophy

The most common form of AMD is geographic atrophy, also referred to as non-exudative or "dry" AMD (Lovie-Kitchin & Bowman, 1985; Kanski, 1994). This condition is characterised by degeneration of localised areas of the retinal pigment epithelium and the neural retina without a break in Bruch’s membrane. The IAESG definition of geographic atrophy requires the presence of:

“any sharply delineated roughly round or oval area of hypopigmentation or depigmentation or apparent absence of the RPE in which choroidal vessels are more visible than in surrounding areas that must be at least 175µm in diameter on a colour slide (using a 30° or 35° camera)”.

The foveal centre is often spared initially to leave a characteristic horseshoe-shaped lesion, but most patients go on to develop an absolute central scotoma (Sarks et al., 1988). Peripheral retina remains healthy and is unaffected by geographic atrophy (Sunness et al., 1985).

The hydroconductivity of Bruch’s membrane reduces with age, secondary to age-related thickening and structural changes within the membrane (Marshall et al., 1998). This process contributes to the presence of drusen and reduces the metabolic exchange between the choroid and RPE. This process is thought to lead to geographic atrophy, although the exact pathogenesis is unknown (Bird, 1996). It is important to note that drusen can occur without atrophy; they are observable in at least 10% of individuals over 65 years of age (Bressler & Gills, 2000) and do not cause vision loss per se (Sunness et al., 1988).

Patients with this form of AMD generally present complaining of a slow onset of visual impairment, often over a time scale of years rather than months (Sarks et al., 1988; Sunness et al., 1995a). No treatment is available to patients with geographic atrophy. (Kanski, 1994; Bird, 1996; Bird, 1997).

1.2.1.3 Exudative AMD

Exudative, neovascular or “wet” AMD is characterised by sudden, acute loss of visual acuity and accounts for about 10% of cases of AMD (Kanski, 1994).
Neovascular membranes from the choriocapillaris break through Bruch's membrane into the sub-RPE space. These membranes can bleed, causing detachment of the sensory retina. This blood can travel into the subretinal space, causing a proliferation of RPE and retinal glial cells which in turn leads to a disciform scar.

Choroidal neovascular membranes can be classified as being classic or occult. Classic lesions develop between the retinal pigment epithelium and the subretinal space (Pauleikhoff et al., 2003a) and are characterised by the lesion being well defined on early fluorescein angiography images. In contrast occult lesions occur beneath the RPE in the outer layers of Bruch's membrane. These membranes lead to multiple hyperfluorescent areas on fluorescein angiography.

In some circumstances the RPE can detach without haemorrhage, due to the build up of other fluid in the sub-RPE space. Both haemorrhagic and non-haemorrhagic forms of exudative AMD are thought to be linked to the build up of debris in Bruch's membrane (Bird, 1997).

The IAESG defines exudative AMD as being the diagnosis when any of the following five signs are present: RPE detachment; subretinal or sub-RPE neovascular membrane(s); epiretinal, intraretinal, subretinal, or sub-pigment epithelial scar or glial tissue or fibrin-like deposits; subretinal haemorrhages unrelated to other retinal vascular disease; or hard exudates within the macular area related to any of the above, and not related to other retinal vascular disease.

Although many medical and surgical treatment options for exudative AMD have been used experimentally (Chong & Bird, 1998; Ciulla et al., 1998; Chakravarthy & MacKenzie, 2000), only two are currently in widespread use: laser photocoagulation and photodynamic therapy.

1.2.1.4 Laser photocoagulation in exudative AMD
Photocoagulation using argon green (wavelength 514.5 nm), krypton yellow (568 nm), krypton red (647 nm) or frequency doubled Ng-YAG (532 nm) lasers can destroy neovascular membranes. Only well defined lesions are amenable to
In suitable patients the risk of severe visual loss over a three year period can be reduced by a factor of 1.4 with photocoagulation (Macular Photocoagulation Study Group, 1986).

Photocoagulation destroys normal retinal tissue, hence the need for a small spot size (100-200 μm) and a short duration to avoid accidental foveal burns caused by sudden eye movements (Pauleikhoff et al., 2003b). Photocoagulation is appropriate in only certain cases (Pauleikoff et al., 2003b), and central fixation is unlikely to be maintained after treatment (Fasce et al., 1996).

1.2.1.5 Photodynamic therapy (PDT) in exudative AMD

In order to reduce damage to healthy retina, photodynamic compounds such as verteporfin (benzoporphyrin derivate monoacid A, e.g. Visudyne™, Novartis Pharmaceuticals, Basle, Switzerland) can be activated by a diode laser to create a photochemical effect in areas of neovascularisation only. Frequent retreatment is required (Bressler, 2000). Results of a multicentre randomised study indicate that for predominantly classic subfoveal membranes visual acuity was preserved in 60% of patients treated (compared to 31% of those in the placebo group) for two years after initial treatment (Bressler, 2001). These results appear to be sustained by the three year follow-up stage (Blumenkranz et al., 2002).

The current guidelines of the Royal College of Ophthalmologists recommend the use of PDT by medical retina specialists only, in the presence of classic or predominantly classic subfoveal neovascular membranes when visual acuity is 6/60 or better (PDT Working Party, 2001). The National Institute for Clinical Excellence has determined that NHS centres may only offer PDT to patients with fully classic lesions, except in the case of clinical trials where patients with predominantly classic membranes may be treated.
Figure 1.2. Pictorial representations of AMD. Top: Geographic atrophy. Bottom: Exudative AMD. Both pictures reproduced from the homepage of the Macular Degeneration Center, Wilmer Eye Institute, Johns Hopkins University, Baltimore, MD, USA. www.wilmer.jhu.edu/mdp/whatismd.html. Accessed on 21 February 2003.
### 1.2.2 Juvenile and early-onset macular diseases

A range of conditions can lead to macular lesions in patients who are too young to develop ARM or AMD, such as those displayed in table 1.1 below.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Typical age of onset</th>
<th>Typical aetiology</th>
<th>Area of lesion</th>
<th>Typical VA and prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stargardt disease (Group 1)</td>
<td>Childhood/young adulthood</td>
<td>Genetic (AR)</td>
<td>Whole fundus</td>
<td>To 6/60. No recovery.</td>
</tr>
<tr>
<td>Stargardt disease (Group 2)</td>
<td>Childhood/young adulthood</td>
<td>Genetic (AR)</td>
<td>Macula</td>
<td>To 3/60. No recovery.</td>
</tr>
<tr>
<td>Stargardt disease (Group 3)</td>
<td>Childhood/young adulthood</td>
<td>Genetic (AR)</td>
<td>Whole fundus</td>
<td>To 3/60. No recovery.</td>
</tr>
<tr>
<td>Stargardt disease (Group 4)</td>
<td>Childhood/young adulthood</td>
<td>Genetic (AR)</td>
<td>At flecks only</td>
<td>Good, unless foveal fleck. No recovery.</td>
</tr>
<tr>
<td>Best disease</td>
<td>Childhood/young adulthood</td>
<td>Genetic (AD)</td>
<td>Macula</td>
<td>To 3/60. No recovery.</td>
</tr>
<tr>
<td>Adult foveomacular vitelliform dystrophy</td>
<td>Fourth or fifth decade</td>
<td>Genetic (AD)</td>
<td>Macula</td>
<td>Mild metamorphopsia only.</td>
</tr>
<tr>
<td>Cone dystrophy</td>
<td>Childhood to middle age</td>
<td>Sporadic; Genetic (AD, X); 2o to e.g. Batten's disease</td>
<td>Macular and paramacular areas</td>
<td>To 6/60.</td>
</tr>
<tr>
<td>Central serous retinopathy</td>
<td>Young adulthood to middle age</td>
<td>Sporadic</td>
<td>Macula</td>
<td>To 6/12, generally recovers.</td>
</tr>
<tr>
<td>Cystoid macular oedema</td>
<td>Infants to old age</td>
<td>2o to cataract surgery, diabetes, BRVO, nicotinic acid retinopathy.</td>
<td>Macula</td>
<td>Generally recovers to 6/9 or better.</td>
</tr>
<tr>
<td>Punctate inner choroidopathy</td>
<td>Young adulthood</td>
<td>2o to multifocal choroiditis</td>
<td>Macula</td>
<td>Good, generally recovers.</td>
</tr>
<tr>
<td>Myopic maculopathy</td>
<td>Middle age</td>
<td>2o to high myopia</td>
<td>Macula</td>
<td>To 6/60, no recovery.</td>
</tr>
</tbody>
</table>

Table 1.1. Typical ages of onset, aetiology, site of lesion, function and prognosis of selected juvenile and early onset macular diseases. AR: Autosomal recessive; AD: Autosomal dominant; X: X-linked; 2o: Secondary. Sources: Gass, 1997; Kanski,
For the purposes of this study, only those diseases which are not caused by another disease process, which affect the macular region only and with no subsequent recovery of function are discussed; Stargardt disease and Best disease. These conditions are described in more detail below.

1.2.2.1 Stargardt disease

Stargardt disease is an inherited macular dystrophy which generally leads to reduced vision in the first or second decades. Fundus flavimaculatus is used as a synonym by some authors (Gass, 1987; Newsome & Blacharski, 1988), although others reserve this term for later-presenting Stargardt disease (Kanski, 1994). Stargardt disease affects around 1 in 10,000 people in the USA (Newsome & Blacharski, 1988).

Fundoscopy often shows yellow “flecks” in the RPE which are similar in appearance to drusen but more variable in terms of size, shape and distribution. Fluorescein angiography shows these flecks to be non- or partially-fluorescent, as opposed to drusen which are hyperfluorescent; and excessive lipofuscin within the RPE prevents clear visualisation of choroidal features and the fundus is darker.

Four groups of patients with Stargardt disease have been identified. Patients in group 1 have vermillion fundi and hidden choroidal fluorescence in fluorescein angiography; group 2 Stargardt disease includes those with atrophic maculopathy (with or without flecks), group 3 patients have maculopathy with signs and symptoms of retinitis pigmentosa, whilst in some cases (those said to have Group 4 Stargardt disease) flecks are present but there is no macular atrophy (Gass, 1997).

Visual acuity in patients with macular involvement deteriorates to between 6/60 and 3/60 (Kanski, 1994). Only 4% of patients in a large case series suffered from VA worse than 3/60 (Rotenstreich et al., 2003). Patients with earlier presenting disease seem to suffer from a quicker deterioration in vision (Rotenstreich et al., 2003). In the absence of maculopathy, visual acuity is normal unless flecks obstruct the foveola (Gass, 1987). About a quarter of patients maintain vision of 6/12 or better (Rotenstreich et al., 2003).
The pattern of inheritance is generally autosomal recessive, although some documented cases show dominant inheritance patterns (Gass, 1987). No treatment options are currently available for Stargardt disease.

1.2.2.2 Best disease

Best disease is an inherited macular dystrophy characterised by distinctive electrophysiological changes and yellow subfoveal pigment. This pigment can form a vitelliform (yolk-like) cyst which may deteriorate to give a "scrambled egg" appearance in the macular region. The cyst may later be replaced by atrophy, a disciform scar or, in rare cases, a neovascular membrane (Kelly & Maumenee, 1999).

Vision loss can vary from mild metamorphopsia to severe impairment of acuity. Visual symptoms usually develop between the ages of 10 and 25, although the electrophysiological changes are apparent from birth.

1.2.3 Subjective complaints of patients with macular disease

The most common complaint of patients with macular disease is difficulty in reading (Krieger, 1967; Faye, 1970; Faye, 1984; Farrall, 1991; Elliott et al., 1997; Dickinson, 1998; Hazel et al., 2000).

A large study examining presenting complaints of consecutive patients at the Kooyong low vision clinic in Melbourne found that reading newspapers was the major concern of patients over 60 years, with nearly 60% of patients complaining of difficulty. Other concerns related to reading included reading books (25%), mail (8%) and magazines (2%). Of course these figures reflect the popularity and importance of these forms of media as well as their relative difficulty (Wolffsohn & Cochrane, 1999).

Mangione and colleagues interviewed 246 patients with low vision and identified 2623 complaints whilst developing the 51-item National Eye Institute Vision Function Questionnaire. They found "reading ordinary print" to be the most
frequent concern in AMD with 70% of patients expressing difficulty (Mangione et al., 1998).

1.2.3.1 Psychological aspects of visual impairment

It is known that patients who experience visual loss experience a similar grieving process to those who have been recently bereaved (Schulz, 1977, Emerson, 1984), and will typically experience stages of shock and depression before adjusting to their visual impairment. “Personality hardiness” has been shown to be the best predictor of successful adaptation to visual impairment, which is related to a sense of being able to control events, having a commitment to oneself and dependents and accepting the loss of vision as a challenge rather than a threat (Robbins & McMurray, 1988).

Williams and colleagues interviewed 86 AMD patients and found quality of life to be impaired and emotional distress significantly increased when compared to age-matched subjects without macular disease. They found the psychosocial impact of macular disease to be as severe as that experienced by sufferers of chronic obstructive pulmonary disease and AIDS (Williams et al., 1998). Patients with newly diagnosed MD were more distressed than those who had time to come to terms with their visual impairment. Interestingly more distress and anxiety was reported by patients with monocular AMD than those legally blind in both eyes, perhaps suggesting that the fear of bilateral MD is more disabling than the reality.

1.2.4 Current approaches to the rehabilitation of patients with macular disease

As macular disease is a largely untreatable condition which often leads to severe visual impairment, rehabilitation of patients is a priority.

1.2.4.1 Low vision assessment

It is important to ensure that the optimal refractive correction is given to all patients. In many circumstances magnifiers can be used to enable reading or other specific tasks (Virtanen & Laatikainen, 1991; Dickinson, 1998; Margrain, 2000). In the UK, the majority of low vision assessments take place in hospital eye departments.
A full description of low vision assessment is beyond the scope of this text. However, examples of the type of magnifiers available, and their approximate power range, are given in table 1.2. Visual training in macular disease is discussed in section 1.6 below.

<table>
<thead>
<tr>
<th>Type of magnifier</th>
<th>Approximate range of magnification available</th>
</tr>
</thead>
<tbody>
<tr>
<td>High power reading spectacles/</td>
<td>to 12x</td>
</tr>
<tr>
<td>hyperoculars</td>
<td></td>
</tr>
<tr>
<td>Non-illuminated hand magnifiers</td>
<td>to 20x</td>
</tr>
<tr>
<td>Non-illuminated stand magnifiers</td>
<td>to 20x</td>
</tr>
<tr>
<td>Illuminated hand magnifiers</td>
<td>to 10x</td>
</tr>
<tr>
<td>Illuminated stand magnifiers</td>
<td>to 30x</td>
</tr>
<tr>
<td>Near vision telescopes</td>
<td>to 8x</td>
</tr>
<tr>
<td>Distance vision telescopes</td>
<td>to 20x</td>
</tr>
<tr>
<td>Near CCTV systems</td>
<td>to 50x</td>
</tr>
<tr>
<td>Distance CCTV systems</td>
<td>to 50x</td>
</tr>
</tbody>
</table>

Table 1.2. The maximum magnification of certain low vision devices. Sources (Gill & Silver, 2001), manufacturers’ data from Telesensory Corp., CA, USA and Enhanced Vision Systems Ltd., CA, USA.

1.2.4.2 Non-optical aids

Many non-optical aids are available to help patients with activities of daily living. These include large print books, kitchen aids, speaking watches and newspapers on tape. Text enlargement software and voice reading programs mean that access to information technology and the internet can be provided. Mobility can be improved by the use of a cane and appropriate training.

1.2.4.3 Social support

Social support is offered by hospital based medical social workers, local sensory impairment teams affiliated to councils and local support groups. In addition, national charities such as the Royal National Institute for the Blind and the Guide Dogs for the Blind Association exist to support people with any form of visual impairment.

1.2.5 The benefit of rehabilitation in macular disease

It is well documented and unsurprising that the provision of low vision aids will improve visual acuity (Temel & Kazokoglu, 1991; Wu et al., 1995). One study
found that nearly 90% of a large sample of low vision patients were able to read N8 size print with appropriate low vision devices (Margrain, 2000). Further, self-reported task performance has been shown to improve with the prescription of low vision aids in 150 of 152 patients. 82 of these patients (54%) described their low vision aids as "very useful" (Scott et al., 1999). As Scott’s study used interviews rather than anonymous questionnaires, results may have been biased by patients’ eagerness to please the interviewer (the “Hawthorne effect” (Wickstrom & Bendix, 2000)). In a similar study, a questionnaire was sent to 576 low vision patients in Germany (Rohrschneider et al., 2002). More than 90% of patients that responded reported high satisfaction with their low vision aids but the response rate was only just over 50%. A serious limitation of this study is, of course, that patients who are able to use their magnifier are far more likely to be able to fill in and return a questionnaire.

It is more difficult to quantify whether quality of life is improved by the provision of low vision aids. In a review of sixteen papers describing the outcomes of low vision rehabilitation, Raasch and colleagues found none which adequately assessed quality of life measures (Raasch et al., 1997).

A rigorous prospective randomised controlled trial to determine quality of life with low vision rehabilitation is being performed in Manchester (Russell et al., 2001).

1.2.6 Summary

Macular disease is a common, debilitating disease which remains largely untreatable. Rehabilitation of macular disease patients is largely based on the prescription of magnification and non-optical aids.

This thesis will provide information on the natural course of adaptation to macular disease, which will enable clinicians to counsel patients more efficiently on the likely development of their symptoms. By studying the behaviour of patients who successfully adapt to MD, it may be possible to advise people who develop MD on the best viewing strategies to use.
The principal adaptive strategy used by patients with central scotomas is to adopt an eccentric preferred retinal locus, which is described in the following section.

1.3 The preferred retinal locus

During fixation, there is some retinal motion due to involuntary eye movements such as physiological nystagmus, drifts and microsaccades as well as correcting movements to compensate for motion of the head (Steinman et al., 1982; Carpenter, 1988). In those without eye disease, the locus of fixation always lies within the foveola.

If there is damage to the foveal region due to macular disease, this locus of fixation may be actively or passively shifted to a healthier retinal area in order to maintain best possible vision. Many patients exhibit one discrete “preferred” retinal locus (PRL) at a para- or extra-foveal location (Timberlake et al., 1986; White & Bedell, 1990; Schuchard & Raasch, 1992; Guez et al., 1993).

1.3.1 Assessment of the PRL

Several devices can be employed to monitor visual behaviour in macular disease, including fundus cameras (White & Bedell, 1990; Nilsson et al., 1998), infra-red eye trackers (Bullimore & Bailey, 1995) and scleral search coils (Cummings et al., 1985; Whittaker et al., 1988). However in recent years the instrument of choice has been the scanning laser ophthalmoscope (SLO).

1.3.1.1 The scanning laser ophthalmoscope

Scanning laser ophthalmoscopes suitable for ophthalmic use have been available for around 2 decades (Webb et al., 1987). Common ophthalmological uses of the SLO include optic disc tomography, imaging of the retina and ocular blood flow measurements. Retinal imaging is performed using an infra-red laser. A video recorder or personal computer can record the image from the SLO for retrospective analysis.
Modern scanning laser ophthalmoscopes work on a confocal principle to reduce the detection of scattered light and to increase image contrast (White & Amos, 1987; Woon et al., 1992). Briefly, a pinhole aperture ensures that the illumination and detection systems of the ophthalmoscope are coincident at any given time. This reduces image degradation from light scatter from structures which are not being observed. Only a small area of the retina is illuminated at once, and the illumination system scans the retina by use of a rotating mirror. Figure 1.3 shows the principal components of the SLO.

![Figure 1.3. Principal components of the scanning laser ophthalmoscope. Dashed line represents the path of the laser beam entering the eye. (After Woon, 1992).](image)

Assessment of the PRL and other psychophysical testing require the addition of a visible laser such as a helium-neon (HeNe) laser ($\lambda=630$ nm) to produce stimuli (Mainster et al., 1982; Webb et al., 1987; Wolf, 1997). The HeNe laser has the capacity to display any monochromatic image which can be produced on a computer monitor such as words or simple images. Targets can be stationary or moving. Because of the real time retinal image provided by the infra-red laser, stimuli can be placed on a known part of the retina. Therefore, the SLO can be used to assess exactly which part of the retina the patient is using for certain tasks.

Another use of the SLO in the assessment of macular disease is microperimetry, which can exactly define the location, area and depth of the scotoma. For this technique, a stimulus is presented at a known retinal location and the patient responds when they see the stimulus by means of a button press. The retinal image is then frozen and the investigator places a cursor over a retinal landmark such as a vessel bifurcation. Superimposition of these images can map “seeing” and “non-seeing” retinal areas.
Unlike conventional perimetry, which only determines the location of any non-seeing area with respect to the centre of fixation, SLO microperimetry elicits the exact retinal location of any scotoma. For this reason the SLO is invaluable in determining scotoma characteristics in patients who do not display central fixation.

The only commercially available SLO with the extra HeNe laser necessary for microperimetry and psychophysics was the SLO-101 produced by Rodenstock of Germany. Unfortunately this device is no longer produced.

1.3.1.2 Choice of fixation target

Many different targets have been used to assess PRLs: squares (Timberlake et al., 1986), numbers (Guez et al., 1993), 3-letter syllables (Timberlake et al., 1987), a grid of letters (Culham et al., 1992) words (Duret et al., 1999) and scrolling text in a variety of directions (Culham et al., 1992). Culham and colleagues recommended that only letters with orthogonal strokes (E, H, I, F etc.) be used to avoid artefacts from curved or diagonal lines within the raster.

Schuchard and Raasch compared different types of central and paracentral fixation targets including a 1° central fixation cross, a 12° cross with a 6° central gap and a diamond pattern consisting of four squares (height 10 minarc) arranged at both 3° and 7° separation. They found the diamond fixation target was the most difficult for all subjects to observe and led to the least stable fixation in both normal subjects and patients (Schuchard & Raasch, 1992).

1.3.2 Position of the PRL

Although all studies have used different methodologies and report data in slightly different ways (for example, defining the location of the PRL in visual field space or as a retinal location) it is possible to collate data for 1573 eyes with macular disease by combining 7 different publications (White & Bedell, 1990; Culham et al., 1993; Guez et al., 1993; Sunness et al., 1996; Fletcher & Schuchard, 1997a; Nilsson et al., 1998; Fletcher et al., 1999). Complete data can be seen in table 1.3. In visual field space, 37% of eyes placed the PRL below the scotoma; 34% to the left of the
scotoma; 18% to the right; 6% above; 3% mixed and 1.6% either repeatably placed the target within the scotoma or displayed no obvious PRL. It is important to note that these patients had a variety of diagnoses and were at a variety of different disease stages.

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Number of eyes</th>
<th>PRL location with respect to scotoma (in visual field space)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>BELOW</td>
</tr>
<tr>
<td>White &amp; Bedell (1990)</td>
<td>Fundus camera</td>
<td>42</td>
<td>86%</td>
</tr>
<tr>
<td>Culham et al (1993)</td>
<td>SLO</td>
<td>6</td>
<td>33%</td>
</tr>
<tr>
<td>Guez et al (1993)</td>
<td>SLO</td>
<td>40</td>
<td>15%</td>
</tr>
<tr>
<td>Sunness et al (1996)</td>
<td>SLO</td>
<td>41</td>
<td>22%</td>
</tr>
<tr>
<td>Fletcher &amp; Schuchard (1997)</td>
<td>SLO</td>
<td>1339</td>
<td>39%</td>
</tr>
<tr>
<td>Nilsson et al (1998)²</td>
<td>Fundus camera</td>
<td>6</td>
<td>67%</td>
</tr>
<tr>
<td>Fletcher et al (1999)</td>
<td>SLO</td>
<td>99</td>
<td>-</td>
</tr>
<tr>
<td>Weighted mean</td>
<td></td>
<td>1573</td>
<td>37%</td>
</tr>
</tbody>
</table>

Table 1.3. Prevalence of PRL location in visual field space.

1 Central fixation for small objects, below-scotoma fixation for large objects.
2 After rehabilitation training.
3 PRLs above or below scotoma.
4 PRLs both left and right of scotoma.

AMD patients generally place the PRL immediately adjacent to the lesion whereas those with juvenile macular degenerations tend to leave a gap between the boundary of the PRL and the scotoma edge (Timberlake et al., 1986; Sunness et al., 1996).

1.3.2.1 Theoretical best location for PRL

If retinal anatomy is considered, it is more logical to move the fixation locus vertically rather than horizontally in the absence of central vision. This provides an uninterrupted retinal area to fixate with, whereas moving the eye along the horizontal meridian results in both the physiological blind spot and the scotoma masking a line of text. It appears that reading speed is slightly faster when fixation is shifted vertically rather than horizontally although it is difficult to determine...
whether this effect is independent of the type of macular disease: patients with JMD tend to shift their fixation vertically and to have a faster reading speed (Sunness et al., 1996).

Given the choice of moving the eye up or down, looking up (i.e. placing the PRL below the scotoma in visual field space) is theoretically better than looking down. This is due to a slight advantage in retinal cell density (Curcio & Allen, 1990; Anderson et al., 1991) and the fact that lower visual field is of more use in locomotion. In subjects without macular disease, reading is faster in inferior than in superior visual field (Petre et al., 2000)

1.3.2.2 Vertical vs. horizontal PRL location
Most patients choose to fixate horizontally rather than vertically. One explanation given for this horizontal bias in PRL location has been postulated by Sunness (1996). She suggests that as during the development of a “horseshoe” scotoma in geographic atrophy there is often a wider field of vision horizontally than vertically the patient will become accustomed to scanning in the horizontal meridian. Therefore when central fixation is lost in later stages of the disease, the eye naturally scans horizontally in order to see clearly. Unfortunately this would not explain the behaviour of patients with other forms of macular disease.

Horizontal eye movements are made far more frequently than vertical saccades in reading. As most studies have investigated PRL use for near tasks, patients may adopt the strategy which they would for reading; that is, moving the eyes horizontally when a word can not be seen (or has been read).

Another reason for the horizontal bias could be to maintain binocularity: fusional reserves in the horizontal direction are around 20-32Δ as opposed to 2-4Δ vertically (Evans, 1997). Further, Panum’s areas of corresponding retinal loci are horizontally oval (Evans, 1997).

1.3.2.3 Left vs. right PRL location
The perceptual span in reading English is 15 characters to the right of fixation and 4
characters to the left (see section 1.5.1.2 below) so placing the PRL to the right of the scotoma should be advantageous. Investigation of normal subjects with hemifield occlusion corroborates this: word identification and reading speed are better in right visual field than in left visual field (Fine, 1999). Puzzlingly, more patients appear to fixate to the left of their scotoma (see table 1.2). It has been suggested that monitoring where fixation has landed with respect to the previous word is of importance in reading (Guez et al., 1993) but no more convincing reasoning has been expressed in the literature to date. In an unpublished study Guez and colleagues found that the situation is reversed in Arabic readers (i.e. those reading right to left) compared to those with French as a first language. In other words, subjects always read into rather than away from their scotomas (Guez et al., 1995). No investigation of PRL location in patients who read vertical languages such as Cantonese has been described in the literature. This would be of particular interest.

1.3.2.4 Task-dependent selection of the PRL

Many of the theoretical considerations described above assume that reading is the primary visual task of the patient. Of course this is not the case; even the most avid readers spend a large proportion of the time not reading. It may be that fixating to the left of the scotoma is advantageous for navigation, communication, face recognition or other activities of daily living.

1.3.2.5 Attention and the choice of PRL location

Attention is a high-level cognitive process which can reduce the perceptual threshold at a given location or for a given stimulus. Transient attention is involuntary and used to guide express saccades (Steinman et al., 1997); (Mackeben & Nakayama, 1993). In contrast focal attention is a sustained process which can divide attention away from the fovea to a peripheral location (Bashinski & Bacharach, 1980; Mackeben, 1999). Attention does not appear to be symmetrically divided around the peripheral retina; the lower visual field has lower attention thresholds than the superior visual field (He et al., 1996; Mackeben, 1999). As there is no corresponding asymmetry in the primary visual cortex, higher cortical processes are thought to guide attention (He et al., 1996).
Attention is by necessity shifted from the fovea in advanced MD. Some research groups have begun investigations into whether PRL location is linked to areas of highest attention. Fine and Rubin have suggested that variation in attentional fields may be of more relevance in predicting reading speed than visual acuity or scotoma characteristics (Fine & Rubin, 1999c). Altpeter and colleagues have examined attentional fields in patients with early macular disease. Their research indicates that there may be a connection between PRL location and previous areas of better-attending retina (Altpeter et al., 2000). It is tempting to speculate that as these patients’ disease progress, their PRLs may develop at the locations predicted by their attentional fields.

1.3.3 Multiple PRLs*

Initially it was assumed that most patients develop one, well-defined PRL (Cummings et al., 1985; Timberlake et al., 1986; Timberlake et al., 1987). It has been suggested that patients with scotomas larger than 20° are more likely to develop several PRLs than those with smaller lesions (Whittaker et al., 1988).

For example, a case study has reported one patient who exhibits three discrete preferred loci of fixation (Safran et al., 1999); a larger, superior PRL was used for the initial recognition of a word and two smaller horizontal PRLs were used for more acute vision. Another patient has been described with a small left PRL which would be used for all but the longest of words, when a superior locus would be employed (Duret et al., 1999). Interestingly upon microperimetric testing only one PRL would be determined, implying that the choice of PRL is task-dependent.

The view that the choice of PRL is dependent on the size of the object viewed is corroborated by Guez and colleagues who find multiple PRLs in four of 24 patients (Guez et al., 1993). Each of these subjects had a spared area of functioning retina within their scotoma for detailed examination of small targets but used a PRL for other tasks.

* Although the plural of locus is loci and the correct abbreviation would be “PRL,” “PRLs” has been used throughout this thesis for clarity.
Lei and Schuchard revealed two PRLs in 28 patients with macular disease and found that fixation could be switched between these preferred loci by altering the luminance of the stimulus (Lei & Schuchard, 1997). The implication made is that a PRL under high luminance is positioned within a relative scotoma, whereas the PRL for dim objects would be in more healthy, peripheral retina.

There are marked methodological problems with assessing whether patients display multiple PRLs. Although in some circumstances it is obvious that a patient has multiple PRLs (for instance when one horizontally shifted and one vertically shifted PRL is used), at other times it is difficult to determine whether a patient truly has multiple loci or whether fixation remains within one, poorly defined PRL. This problem is described further in section 1.3.6.1 below.

Even with scanning laser ophthalmoscopy it is difficult to know whether a patient is attending with a given retinal point at any time, or indeed whether they can even see the stimulus. This is especially true when analysing data from a reading task. Asking patients to read text aloud on the SLO is not straightforward due to the head motion induced by speaking whilst resting against a chin rest. Further, the word which a subject reads is not necessarily the same one which they are looking at or attending.

For the purposes of this study, the operational definition of a preferred retinal locus is: “a circumscribed retinal area used for fixation of a target for ≥10% of a trial.” Multiple PRLs are described when more than one discrete PRL, as defined above, is used during an episode of fixation.

1.3.4 Awareness of PRL use
To determine whether patients are aware that they are eccentrically viewing when they are using their PRL, White and Bedell (1990) used two different phrases when assessing the PRL of patients with AMD and Stargardt disease. In the first condition patients were asked to “look at the middle of the [target],” whilst in the second condition patients were told to “look directly at the middle of the [target], even if it becomes indistinct or disappears.” In only three of 21 patients did the change of
instruction make any difference; the remaining 18 patients used the same, non-foveal PRL under both conditions.

In a similar experiment, Schuchard and colleagues (1992) found a difference in only 1 of 9 patients when they were asked to move their eye so it was in the best position to see a pericentral target as opposed to “pointing directly at the centre of the target, even if you do not see it very well with your eye in that position.”

Similarly, Culham (1994) found that 6 of 9 patients using an eccentric PRL felt that they were still looking straight ahead. These papers suggest that the ability to lose awareness of the PRL use is a beneficial adaptation. White and Bedell suggest that this phenomenon is a corollary of re-referencing of the oculomotor system.

1.3.5 Fixation stability within the PRL

Human fixation is not precise. Rather, as described at the start of section 1.3, fixation is contained within a retinal locus; in normal subjects within the foveola and in patients with MD within the PRL.

1.3.5.1 The bivariate contour ellipse area

A bivariate contour ellipse has been shown to adequately describe loci of fixation in normal observers (Steinman, 1965). The area of this ellipse (bivariate contour ellipse area, BCEA) gives an indication of fixation stability; larger areas correspond to poorer fixation stability. The size of these areas have been described at the 0.623 (Steinman, 1965; Kosnik et al., 1986), 0.68,(Nachmias, 1959; Culham et al., 1993) or 0.95 levels (Schuchard & Raasch, 1992), the latter areas encompassing a greater proportion of fixation points than the former.

1.3.5.2 Method of recording the BCEA

The method of recording fixation stability will affect the size of the BCEA measured. Gaze is more precise when fewer head movements require correction: fixation is 2 to 4 times more stable when a subject uses a bite-board rather than a chin and forehead rest (Steinman, 1965). By extension, fixation would be expected to be less stable when measurement takes place with a free-head eyetracker than
with the SLO and a chin rest.

1.3.5.3 Range of BCEAs with and without MD
SLO measurement of subjects without macular disease gives a BCEA of around 80-370 minarc² (Steinman, 1965; Kosnik et al., 1986; Culham et al., 1993; Rohrschneider et al., 1995). With AMD, they range from near-normal values to over 13,000 minarc² (Culham et al., 1993; Schuchard & Fletcher, 1994; Rohrschneider et al., 1995).

1.3.6 Limitations of current research into the PRL
Three factors have been frequently overlooked in research into the preferred retinal locus: the problem of multiple PRLs, the effect of the contralateral eye and the duration of the disease.

1.3.6.1 The problem of multiple preferred retinal loci
As discussed in section 1.3.3 above, many patients exhibit multiple preferred retinal loci. Grouping all fixation points together in one locus and measuring this area can underestimate fixation stability. Further, the calculation of a BCEA requires fixation points to be normally distributed along the major and minor axes of the ellipse. For example if a patient has two PRLs and fixation falls within two, well defined areas, construction of two ellipses is required. Recording the number and size of these ellipses would provide a more accurate and useful description of fixation behaviour; that is, fixation stability is good within each of two loci.

Whittaker and colleagues used this approach; they defined subjects as displaying multiple fixation loci by assuming an arbitrary maximum area for each PRL of 3°x3° (Whittaker et al., 1988). No empirical basis for using 3° as the maximum size of a PRL was given. This technique could overestimate fixation stability if the eye was drifting over a wider area without discrete loci being present. Other researchers have observed the retina during fixation but have only described multiple PRLs when very different areas of the retina were used for fixation (Lei & Schuchard, 1997; Duret et al., 1999).
When fixation points do not lie within obvious clusters, it is impossible to determine whether patients are using one, poorly defined PRL or two PRLs which lie close to each other on the retina by visual inspection.

1.3.6.2 The effect of the contralateral eye

The overwhelming majority of patients have two eyes and most will have had good binocular vision before the development of their scotomas. The behaviour of the first eye and the second eye to develop macular disease will be very different for two reasons. First, when only one eye is affected and good vision is maintained in the other eye then there is less incentive for a PRL to develop: patients may prefer to maintain foveal fixation in both eyes to allow some coarse level of binocularity. Second, if patients with monocular or asymmetric macular disease are tested with their better eye occluded then this unnatural situation does not represent their behaviour with both eyes open (Schuchard et al., 1995).

As the SLO only allows assessment of one eye at a time, it will be more informative to assess the better of the eyes, as this eye is likely to determine the fixation behaviour with both eyes open (Schuchard et al., 1995).

There appears to be no consensus over which eye is examined. In some studies it is not stated whether the better or worse eye’s fixation characteristics are being recorded (Culham et al., 1993) whilst in others fixation data from both eyes are taken and they are, incorrectly, classed as independent recordings (Guez et al., 1993; Fletcher & Schuchard, 1997b).

White and Bedell assessed only patients’ “preferred eye” (White & Bedell, 1990). However, recent research indicates that it may be the better eye and not the dominant eye which drives the oculomotor system (Kabanarou et al., 2003).

To overcome this problem, throughout this thesis, only the eye with better vision will be used, which will be defined as the study eye. The other eye will be occluded for all testing of PRL location and position.
1.3.6.3 The duration of disease
White and Bedell noted that patients with a longer history of macular disease "showed oculomotor behaviors qualitatively more like those of normals, although centred about a nonfoveal locus" (White & Bedell, 1990). This study was of a cross-sectional design and had a fairly small cohort size with a large range of disease duration. As macular disease patients are heterogeneous, either a very large cross-sectional observation or a longitudinal study of the sort described in this thesis is required to prove the qualitative statement which White and Bedell make in their 1990 paper.

1.3.7 Conclusion
The location of the PRL appears to be idiosyncratic and many patients use theoretically suboptimal locations for fixation. Some patients use more than one PRL to perform a task. Many patients make an adaptation whereby they lose awareness of using their PRL. Fixation stability is poorer when using a PRL than when using foveal fixation.

This study will examine the development of the PRL in terms of its position and patient awareness of its use. Fixation stability will be measured, and a new quantitative technique will be applied to determine the number of PRLs which are used by patients. The selection of the study eye will be made carefully and the time of vision loss in the study eye will be recorded.

The first hypothesis of this study concerns the development of the PRL. It states that a repeatable PRL will develop. The number of PRLs used will fall from many to one and the fixation stability will improve. Patients will lose awareness of the use of the PRL.
1.4 Eye movement control

It is widely accepted that fixation is moved to an eccentric PRL in most patients with macular disease and no foveal function. For the PRL to really be used as a "pseudofovea", eye movements must be made directly to the PRL.

Von Noorden first suggested that some patients used a point of eccentric fixation as if it were a fovea (von Noorden & Mackensen, 1962). White and Bedell reported that one third of their patients exhibited "complete re-referencing of the oculomotor system" to the PRL. Their criteria included the direction of all saccades to the PRL (without going via the scotoma), holding fixation solely within the PRL, and repeatedly using the same, individual PRL. Von Noorden suggests reserving the term "eccentric fixation" for patients who have managed to make this adaptation, using "eccentric viewing" for those who have not re-referenced their oculomotor system in this way.

"Pseudofoveation" is a term first used by Fuchs in 1922 (Fuchs, 1922) to refer to the re-referencing of the visual system to a new point in patients with hemianopia. In the context of macular disease, the term "pseudofovea" could perhaps be applied to a PRL which has become the reference point for the oculomotor system (as a synonym for Von Noorden's "eccentric fixation").

The characteristics of eye movements made to the fovea and to the PRL are described below.

1.4.1 Foveating eye movements

Saccades which bring an object of interest onto the fovea are remarkably quick, sometimes exceeding 700°/sec (Carpenter, 1988; Whittaker & Cummings, 1990b). Non-foveating eye movements are slower (Whittaker et al., 1991) as are saccades to a remembered target (sometimes referred to as R-saccades), saccades made in the dark and the eye movements of infants (Hallett, 1986; Carpenter, 1988).

After an extensive literature review, Whittaker and Cummings found that the
following criteria need to apply to elicit these fast, foveating saccades:

"(1) saccades are elicited in response to a visual stimulus in the periphery; (2) prior to onset, the exact location of the stimulus is unpredictable; (3) the saccade results in the approximate foveation of the target."(Whittaker & Cummings, 1990b)

1.4.1.1 Saccadic latency

An unusual aspect of saccades is their latency; at least 120 msec passes between the presentation of a stimulus and the start of a foveating eye movement to follow it (Carpenter, 1988; Pitt & Rawles, 1988). Foveating eye movements have a lower saccadic latency than non-foveating saccades (Hallett, 1978) but the latency still exceeds reaction time for other muscular movements. For example, blink latencies are only around 55 msec (Peshori et al., 2001). Carpenter (1988) suggests that saccadic latency is a delay caused by cognitive processes determining whether an eye movement is necessary; that is, is the target interesting enough to observe?

Age has been shown to increase saccadic latency in normal observers by about 1-2 msec/year over the age of 20 (Abel et al., 1983; Carter et al., 1983; Whitaker et al., 1986; Pitt & Rawles, 1988).

1.4.1.2 The number of saccades used to view a target

More than a century ago, Dodge and Cline discovered that subjects make more than one eye movement to foveate any target displaced by more than 15° (Dodge & Cline, 1901). Although they presented this as an aside (and indeed seemed quite irritated by this artefact) it has since been well documented that hypometric saccades are normal when observing targets which are decentred by more than about 10° (Carpenter, 1988). The initial saccade represents about 90% of the eye movement and it is immediately followed by a second, correcting saccade. These correcting saccades do not appear to be visually guided; indeed they still occur in complete darkness or when the target is moved to the end-point of the primary saccade (Carpenter, 1988). However, using more than three saccades to fixate an eccentrically presented target is abnormal (White & Bedell, 1990).
1.4.1.3 **Saccadic velocity**

There is a firm relationship between the amplitude, peak velocity and duration of foveating saccades. The duration: amplitude relationship is approximately:

\[
\text{Saccadic duration (msec)} = 2.2A + 21
\]

Where \( A \) is the amplitude of the saccade in degrees (Dodge & Cline, 1901; Carpenter, 1988). In normal observers, saccades get slightly slower with age (Pitt & Rawles, 1988).

1.4.2 **Eye movements with a central scotoma**

The presence of a scotoma will influence foveating eye movements: true foveating eye movements need to be suppressed or adapted so that “foveating” saccades are directed to the PRL and not the scotoma.

1.4.2.1 **Saccadic latency and velocity**

In normal subjects with simulated central scotomas, saccadic latency has been shown to be nearly doubled when compared to the same subjects without a simulated scotoma (Zeevi & Peli, 1979). Zeevi and colleagues also found that latency reduced towards normal levels with extended practice (14 sessions over a four week period). These subjects never achieved the same saccadic latency for their “pseudofoveating” saccades as for their foveating eye movements, but subjects only practised with a simulated scotoma for the 40 minutes whilst they were in the laboratory. Patients with complete central field loss are, of course, practising non-foveating eye movements continuously.

Unfortunately, it does not appear that patients can reach the same level of latency as age-matched subjects without central scotomas. White and Bedell found that all but one of their patients had longer saccadic latency than age-matched controls (White & Bedell, 1990) and Whittaker found a mean saccadic latency of 402 msec in patients and 298 msec in control subjects (Whittaker et al., 1991). Although the controls were slightly younger than the patients in the latter study, the difference in age is not large enough to account for the differences in latency.

Peak velocity of saccades is reduced in patients with MD when compared to age-
matched control subjects (Whittaker et al., 1991).

1.4.2.2 The number of saccades used to view a target
Some macular disease patients can saccade directly to the PRL with one or two eye movements (White & Bedell, 1990; Whittaker & Cummings, 1990a; Whittaker et al., 1991). White found that fifteen of her twenty-one patients (71%) did not make a saccade to the fovea and directed the target to the PRL with 3 eye movements or less. Interestingly the duration of disease did not seem correlated to the absence of foveating saccades.

McMahon and colleagues examined the number of saccades used when patients were asked to look at each of five letter targets in turn (McMahon et al., 1991). They found that the number of saccades used was doubled in patients with AMD when compared to control subjects. This implies that there is a greater saccadic inefficiency in patients with central scotomas. McMahon has shown a correlation between this inefficiency and a reduction in performance on a reading task (McMahon et al., 1991; McMahon et al., 1993).

Patients with central scotomas perform less well on a visual search task, using more saccades to find a target (Murphy & Foley-Fisher, 1988; Murphy & Foley-Fisher, 1989).

1.4.2.3 Animal models
Heinen and Skavenski used Argon laser photocoagulation to destroy photoreceptors in the macula region of three adult monkeys (Heinen & Skavenski, 1991). Before surgery, the monkeys were trained to make foveating eye movements to a moving LED target and to fixate that target within a set window of 0.9°. Correct trials were rewarded with a squirt of water. After the scotomas were created, the monkeys were re-tested daily to analyse the adaptation to these new scotomas.

On the first post-operative day, the animals used superior retinal PRLs (i.e. placing the PRL below the lesion in visual field space). Fixation stability was far worse immediately after the surgery and stabilised within two days (although it never
reached pre-lesion levels).

The saccadic system took longer to stabilise. One monkey fully adapted within one month, to reach pre-lesion levels of saccadic latency and accuracy. The second animal did not reach pre-lesion characteristics but still displayed an improvement in all saccadic properties and made one saccade to the PRL.

The third monkey did not pseudofoveate: he always made two saccades to the PRL. The first saccade was not to the scotoma but to another retinal location completely. This finding is puzzling; no human studies have shown a similar effect.

This simulation does not exactly recreate macular disease in terms of the scotoma (as the lesion will be a well defined absolute scotoma with no surrounding relative scotoma) or in terms of the disease presentation (humans would very rarely lose central vision in both eyes immediately and simultaneously) but the results from these studies remain of great interest.

In particular, the diversity of recovery amongst the three is remarkable. Given that these animals all experienced identical visual loss and behaved differently, examination of humans who experience a wide range of natural histories is likely to produce very varied outcomes.

1.4.2.4 Accidental laser damage to the macular region

Although accidents with lasers are rare, there are a number of reports in the literature of accidental, laser induced scotomas in human subjects (Henkes & Zuidema, 1975; Zwick et al., 1998; Roider et al., 1999). Zwick and colleagues described two subjects who were exposed to neodymium laser beams of the type used in weapon viewfinders. These patients both developed central scotomas and subsequently used a PRL in supero-temporal retina; that is, below the scotoma in visual field space (Zwick et al., 1998). In a similar manner to laser ablations performed in animals, these lesions are not equivalent to those experienced by patients with advanced macular disease. Further, visual acuity recovered to normal values in these patients.
1.4.3 Conclusion

To return to the definition of “complete pseudofoveation” described in section 1.4 above, patients would need to make saccades to their PRL which displayed all the properties of foveating saccades.

Although the first part of this definition appears to be fulfilled by at least some patients, it appears that these pseudofoveating saccades never possess the same properties as true foveating eye movements. As Whittaker states in his 1991 paper, “patients with macular scotoma suppress rather than adapt a foveating saccade mechanism” (Whittaker et al., 1991).

It is clear that some patients manage to re-reference their oculomotor system more fully than others. It is still unknown why some patients manage so much better than others in adapting to their macular disease.

This study will examine the level of pseudofoveation in a variety of patients and will examine the differences between patients who successfully adapt and those who do less well.

The second hypothesis of this study is that saccadic characteristics will change with time. Saccades will become more efficient (that is, fewer saccades will be made to find a target), foveating saccades will be suppressed and eye movements will be made directly to the PRL rather than to the scotoma.
1.5 Reading

Reading is a highly complex visual task, requiring good resolution, precise eye movement control, stable fixation and higher-order cortical processes. It is unsurprising that patients with macular disease suffer severe difficulties with reading.

The ability to read efficiently is critical for full participation in society. In the older population, particularly those with concomitant hearing loss, it is essential to maintain independence. Difficulty in reading is the most frequent complaint of patients with macular disease (Krieger, 1967; Faye, 1970; Faye, 1984; Farrall, 1991; Elliott et al., 1997; Dickinson, 1998; Hazel et al., 2000).

Reading is not only important in itself, it also a better predictor of performance on a variety of tasks (including everyday activities as diverse as recognising faces and cutting finger nails) than standard clinical tests such as visual acuity and contrast sensitivity measurement (McClure et al., 2000).

To be able to identify the causes of the reduction in reading ability in MD is therefore of great importance. Reading speed will be the major outcome measure for the study described in this thesis.

In order to understand the causes of the deficit in reading which macular disease patients experience it is necessary to first consider some elements of the normal reading process.

1.5.1 Some elements of the reading process

1.5.1.1 The effect of text size and contrast on reading speed

In the first paper of their psychophysics of reading series, Legge and colleagues measured the effect of character size on reading speed. They found that in normal observers, reading speed asymptotes at around 250 words/minute once text size reaches 0.3° (approximately three times acuity, assuming a visual acuity of 6/5). When text size exceeds 2° reading speed again reduces, although the rate of decline
is slower than when the text size is diminished (Legge et al., 1985a). Psychophysics of reading papers V, VI and XVI address the effect of contrast on reading speed and find that for normal observers reading speed is not reduced until luminance contrast falls beneath 10% (Legge et al., 1987; Rubin & Legge, 1989; Legge et al., 1997). Contrast polarity (i.e. white text on a black background compared to black text on a white background) does not influence reading speed in normal observers (Legge et al., 1985a).

1.5.1.2 Spans, visual and perceptual
Each letter in a word is not fixated individually when reading. To do so would reduce the speed of reading to an unacceptably low level; saccadic latency alone would cut the time to read a five-letter word to around one second. Instead, several letters are processed during each fixation. The width of this “window” of characters which can be identified is referred to as the visual span (O'Regan, 1990; Legge et al., 1997). Controlling the number of characters available to the reader by masking letters and measuring reading time can indicate the size of the visual span. The width of the visual span is around 10 characters in people with normal vision reading high contrast, “normal size” text (Rayner & Bertera, 1979; Legge et al., 1997).

The visual span is measured when reading isolated words. However when reading sentences other parameters are processed such as word length and the spacing between words, so that eye movements can be planned. The width of this window is known as the perceptual span (McConkie & Rayner, 1975; Rayner, 1975; Rayner & Pollatsek, 1989). The perceptual span is asymmetric; in English readers it extends 15 characters to the right of fixation and 3-4 letters to the left. In more complex languages such as Chinese the perceptual span is much smaller (three characters to the right) (Pollatsek et al., 2000) and in right-left languages the span is reversed (in Hebrew, 11 letters to the left and 2-3 letters to the right of fixation) (Deutsch & Rayner, 1999).

1.5.1.3 Eye movements and fixations during reading
Even in scientific text, the average word length is smaller than the visual span (for example, in this introduction mean word length is 5.4 characters). Therefore in
general one fixation per word is sufficient to read fluently. Normal readers make occasional regressive saccades and sometimes skip small words when reading but on the whole follow this pattern (Cummings et al., 1985; Carpenter, 1988), see figure 1.4.

![Figure 1.4. Typical eye movements for a normal subject reading text, showing fixations (F), forward saccades (S) and regressive saccades (R). Horizontal axis shows time, vertical axis shows horizontal position on the page. (After Carpenter, 1988).](image)

The "landing position" of the eye is slightly biased towards the start of the word which is being read (McConkie et al., 1988). Fixation is held at this point for about 220 msec (Rayner, 1978; Rubin & Turano, 1992) before a saccade is executed to the next word. Fixation duration is increased when the word is uncommon (Raney & Rayner, 1995) or ambiguous. For example, in the sentence:

"The port was a great success when she served it,"

the word "port" could refer to a fortified wine or a harbour. Fixation duration is correspondingly increased. However, if the sentence is reordered, to read:

"When she served it to her guests, the port..."  

the ambiguity is removed and fixation time is not increased (Rayner & Frazier, 1989; Rayner & Morris, 1990; Rayner, 2002).

If text is presented one word at a time on a computer screen by the RSVP technique (Rapid Serial Visual Presentation; Forster, 1970) to eliminate the need for eye movements, very high reading rates can be achieved whilst maintaining comprehension. These rates can be as high as 1,652 words/minute (Rubin & Turano, 1992), equating to a processing time of 36 msec/word.
1.5.1.4 Cognitive aspects of reading speed
In addition to the visual and oculomotor characteristics described above, cognitive processes play a large role in determining how quickly people can read. Proficient readers are able to assimilate information more quickly than poor readers, and they display fewer, shorter fixations per sentence, and longer saccades between fixations (Rayner, 1986). It is believed that fast readers are more able to encode information into a conceptual representation from each fixation rather than having a larger visual span (Jackson & McClelland, 1975). Fast readers are also more prone to adapt their scanning routine depending on the text being read (O'Regan, 1990).

In the older population, literacy and reading ability are known to be related to cognitive function on other tests such as the mini mental state exam, attentional tests, verbal learning skills and memory (Barnes et al., 2004).

1.5.2 Reading with macular disease
Patients with low vision display severe impairment of reading speed (Krischer & Meissen, 1983; Legge et al., 1985b). In particular, a very dramatic reduction in reading speed is found in the presence of a central scotoma (Legge et al., 1985b; Wensveen et al., 1993; Bullimore & Bailey, 1995; Bowers & Reid, 1997; Fine & Rubin, 1999a).

Legge has suggested that three independent factors are taken into account when considering low vision reading: text parameters such as size, font and contrast; ocular factors; and non-visual factors such as linguistic capacity and motivation (Legge, 1991).

Manipulation of text parameters and non-visual factors are beyond the scope of this thesis, so only ocular factors will be considered below.

1.5.2.1 Visibility: reduction in visual acuity and contrast sensitivity
If the loss of visual acuity alone were responsible for the problems macular disease patients experience in reading then given appropriate magnification, a normal or near-normal reading speed should be obtained. This is not the case: for example
Legge's work of 1985 revealed a median peak reading rate of 25 words/min in patients with central field loss even when reading very large characters (of 12-24°). Visual acuity has been shown to be a poor predictor of reading speed in a number of studies, accounting for between 10 and 40% of the variance in reading speed between macular disease patients (Krischer et al., 1985; Legge et al., 1992; Bullimore & Bailey, 1995; Fletcher et al., 1999).

Contrast sensitivity reduction cannot account for the variation in reading speed (Rubin, 1986; Legge et al., 1992; Bullimore & Bailey, 1995), although patients with better contrast sensitivity do tend to read more quickly than others. In their review paper, Whittaker and Lovie-Kitchin suggested that a contrast reserve of 3:1 is required for fluent reading (that is, the contrast of the print needs to be three times the patient's contrast threshold) and that as much as 11:1 is needed to reading at a "high fluent" rate of 170 words/minute (Whittaker & Lovie-Kitchin, 1991).

1.5.2.2 Number of characters seen: reduction of the visual span and the presence of the scotoma

The presence of a scotoma will reduce the number of letters which can be seen in one fixation in a variety of ways. If the subject views the text directly then the central characters will be masked by the scotoma, whilst if they adopt a PRL then the legibility of characters further from fixation may be reduced by the poorer resolution ability and contrast sensitivity of the peripheral retina. As text size increases then the effective width of the visual span shrinks: Legge, Ahn, Klitz and Luebker demonstrated that increasing text size by a factor of six halves the number of characters in the visual span (Legge et al., 1997). In the same paper, the length of each fixation was examined. Patients with low vision exhibited longer fixation durations than normal subjects. The results mimicked those seen for normal subjects reading words at reduced luminance contrast, which is known to reduce visual span.

Bullimore and Bailey (1992) found that the number of forward saccades increased in patients with MD. This reinforces the theory that visual span is smaller and that fewer letters can be processed at one fixation in patients with central field loss. However, they did not find an increase in fixation duration, apparently contradicting the findings of Legge and colleagues. It should be remembered that Legge's group
examined patients with a variety of diagnoses to account for their low vision, not just macular disease.

To examine the effect of a scotoma presented in the centre of a word, as may occur in patients who have not developed a PRL, Rayner and Bertera examined the effect of a simulated scotoma on reading speed. They found that a gaze-contingent mask which occupies the area of just one letter halves the reading speed (Rayner & Bertera, 1979).

Fine and Rubin repeated this experiment with scaling of the letter size to counteract the effect of peripheral visual acuity limiting reading speed (Fine & Rubin, 1999b). Although the fall-off in reading speed they found was not as dramatic as that reported by Rayner, they still found a significant reduction in reading speed even for the smallest mask size. Fine and Rubin also report that for smaller simulated scotomas (<7.5° diameter) the number of letters masked had a more significant effect on reading speed than the size of the mask per se. This suggests that the greatest possible magnification should be offered to patients with small scotomas.

Visual span is artificially reduced by the physiological blind spot when a horizontally shifted PRL is used. If visual span reduction is the sole explanation for the reduction in reading speed then one would expect reading speed to be better in patients with vertically shifted fixation than those with horizontally shifted PRLs. This is not the case (Fletcher et al., 1999). It would also be expected that the size of the scotoma would be correlated to reading speed which is only true when very large scotomas are included (Cummings et al., 1985) but not in a smaller range of scotoma size (Bullimore & Bailey, 1995).

1.5.2.3 Reduction in eye movement control
As discussed in section 1.4.2 above, eye movement control is impaired in patients with central field loss. For reading, saccadic properties are also impaired: when compared to normal subjects, MD patients make more regressive saccades, more forward saccades and consequently see fewer letters per forward saccade (McMahon et al., 1991; Bullimore & Bailey, 1995). This is also the case for normal subjects
with simulated visual impairment (Bowers & Reid, 1997).

If eye movement control reduces reading speed then when RSVP is used to present words in the periphery, patients should be able to read at normal or near-normal rates. In a series of experiments, Rubin and Turano examined RSVP reading in normal subjects and macular disease patients. They found that although peak reading speed is improved with RSVP reading in MD patients (from a mean of 82 words/minute to 120 words/minute), this improvement is far smaller than that for patients with other causes of low vision (182 to 389 words/minute) and normal subjects (303 to 1171 words/minute) (Rubin & Turano, 1992; Rubin & Turano, 1994).

1.5.2.4 Reduction in fixation stability and the use of a PRL
Macular disease patients have poor fixation stability (Culham et al., 1993) which will lead to retinal image motion. Simulation of retinal image motion in normal observers is known to severely reduce visual acuity (Bedell et al., 1997). It seems reasonable to assume that impaired fixation stability may reduce reading ability in a similar fashion in MD patients. Rohrschneider et al (1995) found that “functional impairment” was associated with decreased fixation stability. Rohrshneider’s group determined fixation stability as being poor only when the standard deviation from the mean fixation point was >3°, which is roughly equivalent to a BCEA of 100,000 minarc². This indicates exceptionally poor fixation stability.

Fletcher and colleagues devised a “PRL scoring” system based on fixation stability, pursuit ability and “saccade to PRL” ability (Fletcher et al., 1993; Schuchard & Fletcher, 1994). They found that this score was superior to visual acuity in predicting reading speed and accuracy in patients with central scotomas.

1.5.3 Conclusion
It is difficult to predict reading speed based on clinical information such as visual acuity (Legge et al., 1992) or fundus appearance, although it is known that the presence of a central scotoma drastically reduces the ability to read (Legge et al., 1985b; Legge et al., 1992; Bullimore & Bailey, 1995).
Undoubtedly, the reduction in reading speed in patients with macular disease is multifactorial. Although reduction in visual span is of paramount importance, many factors, including those discussed in sections 1.5.2.1 – 1.5.2.4 above, are likely to interact to reduce reading speed in this population.

The third hypothesis of this thesis is that the variety of variables recorded in this study will improve prediction of reading speed in patients with macular disease.

This study’s fourth hypothesis is that the adaptive strategies discussed above (the development of the PRL and saccadic changes) will cause reading performance to improve over time.
1.6 Training visual behaviour in macular disease

If it is assumed that patients read more fluently when a stable PRL is used, with one "pseudofoveating" saccade to this locus, then an obvious question is whether patients' visual behaviour can be modified with intervention.

Although there is not a large amount of published research on training in macular disease, many standard low vision textbooks advocate training for patients with central vision loss (Farrall, 1991; Dickinson, 1998). Three different training strategies and the use of prismatic spectacles are described below.

It is important to differentiate between training visual behaviour in macular disease, and training patients in the use of low vision devices. Only training of visual behaviour will be discussed here.

1.6.1 Teaching awareness of the PRL location

A simple method to train patients to use eccentric viewing is the afterimage transfer method, which was initially suggested as a method of overcoming anomalous retinal correspondence in amblyopia (Caloroso, 1972; Ciuffreda et al., 1991). Briefly, the optimal viewing angle for a target is determined within the clinic and a strobe light in flashed directly at this retinal area. The patient is then instructed to superimpose the afterimage on to a variety of targets. An extension of this technique is to ask the patient to track moving objects (Holcomb & Goodrich, 1976). A case series of patients using this method found that errors in tachistoscopic letter recognition were significantly reduced and a subjective improvement was reported by patients given this training (Holcomb & Goodrich, 1976). This study also included a control subject who received no training.

The SLO can be used in training patients with central scotoma both by helping the practitioner determine which retinal area the patient is using for fixation and in increasing awareness of the optimum area for viewing a target (Schuchard et al., 1994).
1.6.2 Teaching the use of an “optimal” PRL.
The selection of PRL has already been discussed. The fact that patients frequently choose a theoretically suboptimal area for fixation of their own accord suggests that if patients were instructed to use a more logical area for fixation then their visual performance may improve. Several methods have been suggested to teach patients to use alternate PRLs (sometimes referred to as “TRLs” or trained retinal loci (Nilsson et al., 1998)). These include reading cards with horizontal bars in between each line of text to facilitate maintenance of the eccentric viewing angle (Goodrich et al., 1985) and computer based systems (Fitzmaurice et al., 1994; Nilsson et al., 1998). A modified typoscope can be used so that the patient is asked to keep macular fixation upon a target deviated from the text being read (figure 1.5). The patient would be asked to fixate the red dot on the frame of the typoscope (which would not be seen if the scotoma is large enough) whilst reading text at an eccentric location (Collins, 1987). This method is usually combined with a steady eye strategy whereby the patient moves the page being read whilst keeping their fixation stable (Dickinson, 1998).

Figure 1.5. A modified typoscope to encourage eccentric viewing (After Collins, 1987.)

Culham and colleagues attempted to train patients to use a TRL with a SLO and found that fixation stability, distance and near visual acuity improved after six
hours' training (Culham et al., 1997). Unfortunately no concurrent reading speed improvement was found. Culham (1994) found that performance at an alternative retinal locus never exceeds performance at the PRL for visual acuity, reading scrolled text or fixation stability.

Nilsson and colleagues have trained many subjects to read with a retinal location shifted vertically from the foveal centre (Nilsson et al., 1998; Nilsson et al., 2003). They defined the optimum PRL as being one below the scotoma in visual field based on their own clinical experience and studies of subjects with normal vision and artificial scotomas (Petre et al., 2000). Unfortunately, patients were each prescribed hyperocular reading spectacles at the same time at the commencement of the training and no data are given in this paper for patients who received these spectacles but not the Nilsson's training. An earlier paper by the same authors included a group who did not receive training, however these patients differed from the control group either by having less severe AMD or having cognitive difficulties (Nilsson & Nilsson, 1986). It is, therefore, impossible to dissociate the increase in reading speed attributable to the hyperocular spectacles (and practice with these) from the improvement due to training per se.

In order for eccentric viewing to be efficient at every viewing distance, the geometric angle of rotation of the eye needs to be constant, so that the PRL is consistently placed upon the visual axis of the eye. However when a normal subject is trained to fixate eccentrically at one distance, the angle of eccentricity of the eye when subsequently fixing on a closer object is greater and when looking closer it is smaller (Yap et al., 1986). Yap and colleagues postulate that, due to the phenomenon of size constancy, patients may decentre their eyes by a set visual angle and not by a constant geometric angle. This would reduce the success of eccentric viewing, and has important implications upon the likely success of training eccentric viewing. Unfortunately to date this hypothesis has not been investigated in patients.

1.6.3 Teaching eye movement control
Training saccadic eye movements has been suggested as a way of improving visual performance in dyslexia (Fischer & Hartnegg, 2000) and even in enhancing sporting
performance in athletes with no visual deficit (Goldberg, 1991; Loran & Griffiths, 2000). When applied to subjects with macular disease, McMahon and colleagues found a limited improvement in reading rate in some patients after a seven-week inpatient rehabilitation program (which also incorporated the prescription of low vision aids and counselling about the nature of the vision problem (McMahon et al., 1993)). Again the lack of a control group is a serious limitation in this study.

1.6.4 The use of prismatic spectacles
Prismatic scanning, or prism relocation therapy, is a means of redirecting the image away from the fovea and onto the PRL. In contrast to the other methods above, the patient must not make any adaptive eye movements to see a target but must instead direct their fovea toward the object of regard. Initial results indicated this technique was remarkably effective, with one study claiming 100% of 59 patients were able to improve their reading acuity with prism relocation therapy (Romayananda et al., 1982). As with many other training studies, no control group was included in Romayananda's study. This problem was addressed in a later study by Rosenberg (1989). 18 of 19 of patients in the treatment group (94%) demonstrated an improvement in visual acuity, visual function or both. However, the same improvement was recorded in 64% of the control group (7/11). Recent research in the UK has not found the use of prismatic spectacles to be of great benefit in patients with AMD (Cacho et al., 2003; Smith et al., 2003).

1.6.5 The use of visual training in macular disease
Some centres, such as the Veteran's Administration in the USA and clinics in Sweden, provide a large amount of visual training in patients with macular disease. All of the techniques described above require many hours of patient contact. In the UK these resources are not available at present. Most practitioners working in NHS (state-funded) low vision clinics will advise patients on the theory of eccentric viewing but will not offer any formal training.

Further scientific reports are required in the field of visual training, preferably of a prospective, double-masked design. The remarkable finding described above that the majority of patients in a control group demonstrated some visual acuity or
functional improvement indicates the degree of scepticism which should be applied to work published without the inclusion of a "sham" group (Rosenberg et al., 1989).
1.7 This study: The development of viewing strategies in macular disease

1.7.1 Rationale
Over the four decades since von Noorden first described eccentric fixation in macular disease (von Noorden & Mackensen, 1962), many studies have increased our understanding of fixation in macular disease. In particular, the development of the scanning laser ophthalmoscope in the 1980s has enabled more complete assessment of the behaviour of patients with MD. However, very little is known about the development of these fixation and eye movement control strategies. With few exceptions, all subjects examined have had long standing macular scotomas who have already developed adaptive strategies to partially ameliorate the symptoms of the disease. A cross-sectional study design can not correct for individual differences in behaviour between patients and does not directly assess the timescale of development of adaptive strategies.

Many authors have suggested a longitudinal, prospective study to examine changes in visual behaviour in patients with new macular disease (Whittaker & Cummings, 1990a; Legge et al., 1992; Schuchard & Fletcher, 1994; Culham, 1994), but to date no human studies have been reported. The only prospective longitudinal study on adaptation to new scotomas published is in the adult macaque monkey (Heinen et al., 1991; see section 1.4.2.3 above). Problems with comparing the performance of animals to that of humans with macular disease have already been discussed.

There remains a gap in our knowledge concerning the time scale over which the visual behaviour of human patients with macular disease adapts. Knowledge of the natural course of adaptation to MD would help in the rehabilitation and counselling of patients with the disease. This information would also be of benefit in future studies which examine training programs or treatment regimes in patients with MD.

1.7.2 Introduction to this project
This thesis describes a longitudinal study of visual behaviour in human macular disease and builds upon the cross-sectional studies of White, Whittaker, Bullimore, Sunness, Culham and others to contribute to our understanding of the adaptations
which patients make to this debilitating disease.

Patients have been recruited at the point of developing a scotoma in their second affected eye. The longitudinal nature of this study has made it possible to investigate the timescale and pattern of the development of adaptive strategies. In particular the development of the preferred retinal locus, changes in the characteristics of saccades and the re-referencing of the oculomotor system are analysed.

1.7.3 Aims
The broad goals of this study can be summarised under the following three aims.

1. To examine and quantify the adaptive strategies which are naturally adopted by patients who have lost central vision due to macular disease, with particular reference to fixation behaviour, the number of preferred retinal loci used and the use of non-foveating saccades.

2. To determine the changes in these adaptive strategies which occur for a period of twelve months immediately following visual loss in the second eye to lose central vision.

3. To determine the relative utility of each of these adopted strategies, with particular reference to reading speed and change in reading speed.

1.7.4 Hypotheses
1.7.4.1 Hypothesis 1: A PRL will develop
After scotoma development, patients will develop a consistent preferred retinal locus. The number of different PRLs used will reduce from many to one and fixation stability will improve. Patients will lose awareness of the use of the PRL.

1.7.4.2 Hypothesis 2: Eye movement control will improve
The number of saccades used to locate a target will reduce over time. Foveating
saccades will be suppressed and eye movements will be made directly to the PRL rather than to the scotoma. Eye movement control will become more efficient when reading; with time, fewer saccades will be required to read a sentence, and the number of regressive saccades made during a reading task will fall.

1.7.4.3 Hypothesis 3: Reading speed will be predicted more precisely
The measurement of clinical, fixation and eye movement variables in this study will improve the prediction of reading speed in patients with central scotomas.

1.7.4.4 Hypothesis 4: Functional performance will improve
Reading performance will improve over time, in tandem with the improvements in fixation and eye movement control described above.

1.7.4.5 Hypothesis 5: JMD patients will display superior performance
Patients with juvenile macular disease will make the adaptations described in sections 1.7.4.1 and 1.7.4.2 above more quickly and more completely than will those with AMD.
Chapter 2: General method

2.1 Patient selection

Patients were recruited from the medical retina, low vision and accident and emergency clinics at Moorfields Eye Hospital (MEH). Control subjects were friends, colleagues or relatives.

2.1.1 Inclusion and exclusion criteria

2.1.1.1 Inclusion criteria for patients

The primary inclusion criterion was that patients must have experienced significant vision loss in their better eye within the two weeks prior to recruitment, due to AMD, Stargardt disease with macular involvement or Best disease. The vision loss must have been significant (a deterioration of at least 0.2 logMAR units, or a severe limitation of reading or functional performance) and sudden (deterioration took less than one week). Patients had to be able to read English as a first language. Participants had to be at least 16 years old and capable of giving informed consent.

2.1.1.2 Exclusion criteria

Specific exclusion criteria included the presence of diabetes mellitus, concomitant eye disease (other than visually insignificant cataract) or a history of neurological or psychiatric disease. If patients' neurological status was questionable, a mini mental state exam was performed.

All patients recruited into this study had either been deemed ineligible for medical or surgical treatment by their ophthalmologist or had declined such treatment.

After data collection commenced, it became clear that good calibration of the eyetracker could not be achieved in patients with acuity less than 6/60 in their better eye. Subsequently this became an exclusion criterion. In addition, two patients who were referred into the study did not have an absolute scotoma which could be identified on microperimetry. They were also excluded.
2.1.1.3 Inclusion criteria for control subjects
Control subjects had vision of 0.1 logMAR or better in both eyes (with spectacle correction if appropriate) and no evidence of ophthalmological disease on ophthalmoscopy (and other tests as indicated). They had no history of ophthalmological, neurological or psychiatric disease. All spoke and read English as a first language, were aged over 16 years and gave their informed consent. Control subjects were age-matched to assessed subjects in two groups: an older and a younger control group. No attempt was made to match intelligence or educational background between patients and control subjects.

2.1.2 Visit schedule
Patients attended for a baseline assessment within one week of recruitment (i.e. within three weeks of their visual loss). Subsequent appointments were arranged one month, three months, six months and twelve months after the baseline visit. In addition, some patients recruited in the early stages of the study attended for an eighteen month follow-up visit. Control subjects attended twice: at baseline and one year later. Participants’ travelling expenses were paid, and a voucher for the hospital cafeteria was given at each visit.

2.1.3 Discharge point from study
Patients were discharged before their twelve month appointment when the macular disease in the study eye deteriorated. Deterioration was defined as an increase in scotoma area of 0.5 disc areas or more, or a loss in visual acuity of 0.2 logMAR units (2 lines). Further, patients were removed if their study eye became the worse of the two eyes (i.e. if the visual acuity in the contralateral eye improved).

2.1.4 Ethical committee approval
The MEH ethics committee approved the study in November 2000, before recruitment began. The study was given the ethical reference code “CULL1003.” The study conformed with the Declaration of Helsinki. All patients gave their informed consent after reading a consent form. In the case of patients under 18 years of age, the patient and a parent both gave consent. A copy of the consent form can be found in Appendix 2.
2.2 General method

This section explains the methods used in this study. More detailed protocols can be found in appendix 2 of this thesis.

2.2.1 Definition of study eye
The "study eye" was defined as being the eye with the better visual acuity. The contralateral eye was occluded with a simple eye patch for all tests except for the low vision assessment (which was performed binocularly) and distance visual acuity measurement (which was performed monocularly in each eye).

2.2.2 Monitor setup
The PC monitor used (Trinitron GDM-F500R, Sony, Japan) had a white background of 125 cd/m² and a refresh frequency of 85 Hz. The monitor resolution was 800 x 600 pixels for all experiments.

2.3 Clinical method

2.3.1 Refraction
All patients were refracted by a qualified optometrist in accordance with techniques taught on undergraduate optometry courses. Retinoscopy and subjective refraction were performed. Refractive error was defined as the most positive spherical lens and minimum astigmatic correction consistent with best visual acuity (Bennett & Rabbetts, 1989). Spectacles were prescribed if patients appreciated a significant improvement over their habitual distance correction.

2.3.2 Low Vision Assessment
Where satisfactory near visual acuity could not be achieved using a simple reading addition a full low vision assessment was performed as described in standard texts (Dickinson, 1998). Devices prescribed were issued on loan from MEH in accordance with the normal hospital system.
2.3.3 Distance visual acuity measurement
The ETDRS logMAR chart (Lighthouse, New York) was used at 4 metres to measure distance visual acuity in the standard manner (Bailey & Lovie, 1976).
Visual acuity was recorded with the optimal refractive correction. Three different ETDRS charts were used and the same chart was not used on consecutive visits.

2.3.4 Near visual acuity measurement
Bailey-Lovie word reading cards (National Vision Research Institute of Australia, Australia) were used for near visual acuity measurement. An addition of +4.00 DS was made to the distance spectacle prescription and the patient was asked to hold the test card at 25cm. The smallest line of words read with less than two errors was recorded as the near visual acuity. The same card was not used on consecutive visits. Patients were not permitted to use any low vision devices for this assessment.

2.3.5 Contrast sensitivity
Contrast sensitivity was assessed using the Pelli-Robson chart (Pelli et al., 1988) at 1 metre. Results were scored using the method described by Elliott (Elliott et al., 1991).

2.4 Assessment of visual function

2.4.1 Suprathreshold reading speed
Ten 55-character sentences were displayed on the computer monitor. Sentences were randomly selected from a database of over 500 sentences and had similar properties to those used on the MNRead card (Legge et al., 1989) in terms of difficulty and word order*. The sentences had a Flesch-Kincaid Grade level of 4.6. Fourth-grade level text has been recommended for use in consent forms for participation in medical research (Paasche-Orlow et al., 2003).

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* Sentences were supplied by Dr Elisabeth Fine of Harvard Medical School, Mass., USA. Sentences containing US spellings (or references to baseball) were removed.
Sentences were displayed in Times New Roman font over two lines, with word wrap, in the centre of the screen. The left hand side of each line was justified. Sentences were presented at three times threshold visual acuity size as the minimum acuity reserve reported for "high fluency" reading in macular disease patients is 3:1 (Whittaker & Lovie-Kitchin, 1991; Lovie-Kitchin et al., 2000; Massof, 2003). Although it is conceded that higher reading speeds may be possible with larger text, using text of this size also enabled the sentences to comfortably fit upon the screen when viewed from 50cm.

Subjects were asked to read the sentences out loud as quickly as they could without making errors. Timing commenced at the moment the sentence appeared. A keystroke made by the investigator when the last word was read correctly stopped a timer in the computer. A blank screen appeared in between each sentence. If the sentence was read incorrectly then it was excluded from the analysis, unless the patient corrected their error. The mean time to read a sentence was recorded and reading speeds were converted into words/minute for subsequent analysis.

2.5 Laboratory methods

2.5.1 Scanning laser ophthalmoscopy

A Rodenstock SLO (SLO-101, Rodenstock, Germany) was used for all scanning laser ophthalmoscopy in this study. This SLO consists of a 633nm Helium-Neon laser for stimulus display and an infra-red laser of wavelength 780nm for retinal imaging. The SLO can be seen in use in figure 2.1.

Simultaneous video recording was performed during all SLO experiments using a professional mini digital video recorder (BR-DV600E, JVC, Japan) at a frequency of 25 Hz with audio recording.

The scanning laser ophthalmoscope meets the safety criteria of the International Electrotechnical Commission regulation 825 for the safety of laser products and is CE marked.
2.5.1.1 Microperimetry
The size of the dense scotoma was measured using the SLO’s inbuilt microperimetry module (Scotometry v.3.1b, Rodenstock, Germany). A full description of microperimetry can be found elsewhere (Sunness et al., 1995; Varano & Scassa, 1998). Briefly, the patient is asked to fixate a central cross of height 2.5° whilst reporting, by means of a button press, when they see a point target which is presented at a retinal location selected by the investigator. The stimuli used were Goldmann III size targets of intensity 200 cd/m² and were presented for 200 msec. Immediately after stimulus presentation, the retinal image was frozen and the investigator marked a distinctive retinal feature (for example a vessel bifurcation). Superimposition of these images creates a map of seeing and non-seeing retina.

2.5.1.2 Analysis of SLO images
An example of the image produced by microperimetry is shown in figure 2.2. Seen points are represented as dots whilst non-seen points appear as empty triangles. The blue cross indicates the centre of fixation and the red cross the reference point used.
Figure 2.2. An example microperimetry plot.
2.5.1.3 Measurement of scotoma size

Microperimetry images were laser printed. The boundary of the optic disc was traced onto a sheet of acetate paper (CG330, 3M, Texas, USA) and this sheet was superimposed onto the microperimetry image. The area of the scotoma was recorded to the nearest 0.5 disc areas.

2.5.1.4 Analysis of fixation

The habitual location of fixation was recorded when patients had completed the microperimetry task. Patients were asked to look at the central fixation cross for a further thirty seconds whilst no stimuli were presented. The location of the principal PRL was determined in the manner described below. Where patients displayed multiple PRLs, the location of the principal PRL was recorded, being the retinal location where patients fixated for the greatest proportion of the trial. Where fixation was divided equally between multiple PRLs, patients were asked to sit back from the SLO and were reassessed after a few seconds to determine the PRL which patients would select habitually. If ambiguity still existed, videotapes were shown to a medical retina ophthalmologist* who was asked to decide where the principal PRL was. This ophthalmologist was masked from any patient details. The location of the principal PRL was recorded with respect to the scotoma in visual field space, as shown in figure 2.3.

Fixation location was then recorded under two further verbal instructions, which were:

1. “Please look at the red cross in the centre of the screen in front of you”
2. “Please move your eyes so that you are looking straight at the cross, even if it disappears or becomes difficult to see.”

Patients indicated when they had followed each instruction. At this point, digital images were captured using the PC connected to the SLO. As only one retinal image was frozen under each instruction, care was taken to ensure that the point

* Dr Stamatina Kabanarou, Fellow in Medical Retina, Moorfields Eye Hospital and Research Ophthalmologist, Institute of Ophthalmology
selected was within the centre of the locus used under each condition. If the distance between the two centres of fixation was small then retrospective analysis of the video recording was performed to determine whether the two locations lay within one PRL or were within discrete loci. If ambiguity existed then Dr Kabanarou was used as a final arbiter of whether the fixation points lay within the same PRL or within a different retinal area. As in the previous experiment, Dr Kabanarou was blind as to the identity or any clinical features of the patient in question.

The location of fixation was always recorded with respect to the scotoma. The convention used was to describe the fixation location with respect to the scotoma in visual field space (see figure 2.3).

![Figure 2.3. Convention used to describe fixation location (right eye)](image)

2.5.2 Eye tracking

Eye movement data was collected with a SMI Gazetracker (SensoMotoric Instruments, Germany), running EyeLink software (v2.04). Stimulus presentation software was written in-house using commands from the EyeLink library.
2.5.2.1 Calibration and drift correction
Before each experiment, the eyetracker was calibrated and the calibration was validated using the algorithms provided for this purpose. Only trials where the calibration was categorised as "good" by the Eyelink software were included. Calibration is described as "good" when minimal nonlinearity exists when fixating different target positions (maximum ratio of gains = 1.5:1 horizontally, 3:1 vertically (personal communication, SR Research, Osgoode, Canada)).

Drift correction compensates for any slip between the gazetracker headset and the patient's forehead. This was performed in between each set of data collection, and in between each sentence in the assessment of reading.

2.5.2.2 Fixation stability
Fixation stability was measured by asking patients to observe a round target presented in each of five positions: in the centre of the screen, 18° to the left and right and 12° above and below screen centre. These positions were used as they correspond to 100 pixels in from the edge of the screen, so large decentration is possible without the screen edge interfering with the target visibility.

The target was a black circle of 3° diameter with an 18° central white detail, presented against a plain white background on the computer monitor. The target appeared for 10 seconds in each of the five locations, in a randomised order.

Subjects were asked to perform one practice trial at each visit before data were recorded to familiarise themselves with the task.

Data were retrospectively analysed using a Matlab program written specifically for this purpose. Data analysis consisted of four stages. First, the first second of data was removed to allow patients to find the target on the screen. Second, data recorded for 0.25sec preceding and 1 sec following the start of any blinks were removed. Next, eye positions recorded during a saccade (velocity >30°/sec) were removed. Finally, a bivariate contour ellipse or ellipses were calculated using the
equations given in Chapter 3.

2.5.2.3 Saccadic latency, accuracy and peak velocity

Saccadic latency was recorded separately for horizontally and vertically decentred targets. After initial calibration, subjects fixated a central target for ten seconds. As in previous experiments, the stimulus was a 3° black circle with an 18' central detail against a white screen background. The target then disappeared and immediately reappeared 18° to the left or right of the initial target location. After 5 seconds, the new target disappeared and reappeared instantly at the central position. This was repeated to a total of 20 times. The computer randomly presented the stimulus in either the left or right screen position but in each case the next presentation was central.

For vertical saccadic profiles, the experiment was identical apart from the decentred target being 12° above or below the central location.

EDFview software (SensoMotoric Instruments, Germany) was used for retrospective analysis of saccades. Figure 2.4 below shows an example EDFview plot for one second of one target presentation. The blue line represents x-position of gaze (in pixels), the red line indicates y-position and the brown line pupil diameter. The green stripes indicate saccades (defined as eye velocity ≥30°/sec or acceleration ≥8000°/sec/sec). The grey squares are printed for ease of determining time and decentration only.

Properties of the first saccade are printed below the graph. Therefore the following measurements would be recorded from this block:

- Saccadic latency = 281ms
- Number of saccades to fixate target = 2
- Peak saccadic velocity = 390°/sec
Saccades made to the central target were not analysed as saccades to a previously fixated location have different properties (Carpenter, 1988). Mean saccadic latency, mean number of saccades and mean peak velocity was recorded for each position of gaze (left, right, up and down).
2.5.2.4 Eye tracking for reading
Horizontal eye movements were recorded for reading sentences presented under the conditions described above (section 2.4.1). Saccades were analysed using EDFviewX. The total number of forward and regressive saccades was recorded, as was the number of saccades to find the start of each line of text. Figure 2.5 shows an example EDFviewX screen for reading.

Figure 2.5. An EDFviewX screen for a reading trial.
Only horizontal saccades were considered in this analysis, although the vertical eye movement recording was used to determine when patients were looking towards the second line of the text. From the example given in figure 2.5, the number of saccades to find the start of the line was 2 for the first line and 3 for the second line; the number of forward saccades made is 16; and the number of regressive saccades is 11.

2.6 Software used for statistics and data analysis

JMP (v4.0.4, SAS software, Cary, NC, USA) was used for data storage, exploratory analysis, linear regression, survival analysis and some multivariate analysis. Further multiple regression was performed using Systat (Systat software, Richmond, CA, USA). Odds ratios were calculated using JMP with a correction factor to account for non-unity interval values (applied in Microsoft Excel).

Matlab programs were used to sort fixation data and to calculate the global BCEA.

Kaleidagraph (v3.51, Synergy software, Canada) was used for most of the graphs in this thesis.
Chapter 3: Development of statistical method

Section 1.3.6.1 discussed the difficulties of assessing the number of preferred retinal loci used by patients. For the longitudinal study described in this thesis, comparisons need to be made between visits and between patients. A test for the number of PRLs is required, and the characteristics of these PRLs need to be defined. This requires the use of advanced statistical techniques, which are described below.

3.1 Collaboration

The techniques used to analyse multiple PRLs described in section 3.3 below were developed in close collaboration with Miss Michelle Sims (MS) and Dr Rex Galbraith of the Department of Statistical Sciences, University College London. The development of these programs was part of Miss Sims’ MSc degree in statistics. MS also wrote the S-Plus programs used for these analyses. The application of these programs and all data analysis was performed by MDC.

3.2 Fixation stability: The bivariate contour ellipse area (BCEA)

The BCEA describes the area of an ellipse which encompasses a given proportion (P) of fixation points during one fixation trial (Steinman, 1965; see section 1.3.4.1).

When fixation data is normally distributed in both the x and the y dimension, the following formula can be applied to calculate the BCEA:

\[ BCEA = 2k \pi \sigma_h \sigma_v (1-\rho^2)^{1/2} \]  

[Eq. 3.1]

Where: \( \sigma_h \) = Standard deviation of point location over the horizontal meridian
\( \sigma_v \) = Standard deviation of point location over the vertical meridian
\( \rho \) = Product-moment correlation of these two position components
The value $k$ is dependent upon the probability area chosen (see equation 3.2).

\[ P = 1 - e^{-k} \]  

[Eq. 3.2]

where $e$ is the base of the natural logarithm.

Therefore when $k$ is 1 the area describes fixation for 63.2% of the time. For the purposes of this study a $P$ value of 0.68 ($k=1.14$) has been used.

3.3 Analysing multiple loci of fixation

In order to determine how many loci are present within one fixation trial, a test for multimodality is required. Formal statistical tests for detecting the number of multiple components exist (Titterington et al., 1985) but they require the distance between the components to be large. We have used two statistical tests in the assessment of multiple PRLs: the kernel density estimator, which provides an estimate of how many loci are present and the expectation, maximisation algorithm to determine the properties of these PRLs.

3.3.1 The kernel density estimator

The kernel density estimator (KDE) is a nonparametric density estimator which can be used to determine the number of clusters in a set of data (Silverman, 1986). A computer program produced a smoothed kernel plot of the data points using a 50x50 grid and a set window width as suggested by Bowman and Foster (Bowman & Foster, 1992). The number of non-overlapping peaks was recorded as the number of PRLs present.

An example of an ambiguous data set which has been analysed with the KDE is shown in figure 3.1.
3.3.2 The EM algorithm

After performing the KDE calculations, a mixture of component bivariate normal distributions was fitted to the data using the EM (expectation, maximisation) algorithm. The number of discrete peaks seen on the contour plot produced by the KDE was used as the number of components. The EM algorithm returns the estimated parameters of each bivariate normal distribution, the mean position and the standard deviation along the x and y axes, the correlation coefficient, a “local” BCEA for each locus (using equation 3.1) and an estimate of the proportion of data which fell into each locus. The estimated parameters are those for which the log likelihood is highest. The algorithm calculates the value of the log likelihood and also the Bayesian information criterion (BIC) and the integrated classification likelihood (ICL-BIC)(McLaughlan & Peel, 2000). These can be useful to aid model selection (for example to determine the number of components if this is not clear from the KDE plot). The whole process was performed ten times using different starting values in order to check that the estimates converged to the correct final...
values.

Table 3.1 shows the results of the EM algorithm, when applied to the dataset used in figure 3.1. As can be seen, the sum of the local BCEAs is less than half of the value of the global BCEA shown in figure 3.1.

<table>
<thead>
<tr>
<th>PRL</th>
<th>Mean X</th>
<th>Mean Y</th>
<th>SD X</th>
<th>SD Y</th>
<th>Correlation coefficient</th>
<th>p</th>
<th>BCEA (minarc²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-14.9</td>
<td>16.7</td>
<td>7.26</td>
<td>5.16</td>
<td>-0.50</td>
<td>0.36</td>
<td>2400</td>
</tr>
<tr>
<td>2</td>
<td>-13.8</td>
<td>-5.42</td>
<td>6.77</td>
<td>4.45</td>
<td>-0.65</td>
<td>0.31</td>
<td>2500</td>
</tr>
<tr>
<td>3</td>
<td>37.7</td>
<td>-24.9</td>
<td>8.63</td>
<td>6.17</td>
<td>-0.25</td>
<td>0.22</td>
<td>4340</td>
</tr>
</tbody>
</table>

Table 3.1. Description of each PRL returned by the EM algorithm. p=proportion of points in each PRL.

3.4 Application and validation

Data were cleaned using the Matlab program described in section 2.5.2.2 above. This dataset was saved as a text file. A program written by MS using S-Plus (v4.5, MathSoft, Cambridge, MA, USA) was used to run the KDE on the cleaned dataset. If the KDE indicated the presence of multiple PRLs then the number of loci was entered into another S-Plus program which performed the EM algorithm.

Fixation stability was described by recording the sum of local BCEAs and the number of PRLs present.

3.5 Further information on the statistical techniques

This section gives mathematical details of the KDE and EM algorithm. It is taken from the Vision Research paper written by MDC and MS which can be found in appendix 4.
3.5.1 The kernel density estimator

The use of a kernel density estimator in multivariate data is explained in detail elsewhere (Silverman, 1986). Briefly, if a sample of horizontal and vertical observations \( \left( x_1, y_1 \right), \ldots, \left( x_n, y_n \right) \) is collected with joint probability density function \( f(x,y) \)

then the kernel density estimator for bivariate data is:

\[
\hat{f}(x, y) = \frac{1}{nh_xh_y} \sum_{i=1}^{n} K \left( \frac{x - x_i}{h_x}, \frac{y - y_i}{h_y} \right) \quad (i = 1, \ldots, n) \quad \text{(Eq. 3.3)}
\]

Where \( K(x,y) \) is the kernel function, such that:

\[
\int_{-\infty}^{\infty} K(x,y) dx dy = 1
\]

and \( h_x, h_y \) are window widths or smoothing parameters.

We used the following kernel function (Silverman, 1986):

\[
K(x,y) = \frac{1}{2\pi} \exp \left( -\frac{1}{2} \left( x^2 + y^2 \right) \right)
\]

Bowman and Foster suggested the following optimal window widths (Bowman & Foster, 1992):

\[
h_x = \hat{\sigma} n^{-1/6} \quad h_y = \hat{\sigma} n^{-1/6}
\]

where \( n \) is the number of observations and \( \hat{\sigma}_x, \hat{\sigma}_y \) are estimated standard deviations of \( x \) and \( y \).

3.5.2. The EM algorithm

The EM algorithm is a method of calculating maximum likelihood estimates. Let \( y_i \) denote the \((x,y)\) coordinates for the \( i \)th observation. The observed data \( y_1, \ldots, y_n \) can be regarded as incomplete since the components to which they belong are unknown.

If \( z_{ij} = 1 \), \( y_i \) has a probability density function \( f_j(y;\mu_j;\Sigma_j) \), where \( f_j(y;\mu_j;\Sigma_j) \) is a bivariate normal density function with mean \( \mu_j \) (2x1) and convergence matrix \( \Sigma_j \) (2x2). Let \( z_i = (z_{i1}, z_{i2}, \ldots, z_{ik})^T \) denote a multinomial vector indicating which component \( y_i \) is from. That is, exactly one of \( z_{i1}, \ldots, z_{ik} \) equals 1 and the others equal 0. The probability that \( z_{ij} = 1 \) equals \( \pi_j \) (where \( \pi_1 + \pi_2 + \ldots + \pi_k = 1 \)) so \( \pi_j \) represents the proportion of time that the \( j \)th PRL is occupied. A complete data sample is
therefore \( \left( z_1, \ldots, z_n \right) \). It is assumed that all \( n \) observations are independent and have been fully categorised. The complete data log likelihood is:

\[
\ell_C(\theta) = \sum_{i=1}^{n} \sum_{j=1}^{k} z_{ij} \log(p_j f_j(y_i; \mu_j; \Sigma_j)) \tag{Eq. 3.4}
\]

where \( \theta \) denotes the full set of parameters \( \pi_j, \mu_j, \Sigma_j \) for \( j=1,2,\ldots,k \).

The E,M algorithm treats \( z_1, \ldots, z_n \) as missing data. It is an iterative procedure consisting of two steps, E (Expectation) and M (Maximisation).

### 3.5.1.1 The E-step

The E-step calculates the expectation of the complete data log likelihood with respect to the missing data given the observed data \( y \) and current parameter values \( \theta \). The log likelihood is linear in the \( z_{ij} \) so the E step simply replaces \( z_{ij} \) by their expected values \( \pi_{ij} \) given \( y \) and \( \theta \). Thus:

\[
\pi_{ij} = \mathbb{E}(z_{ij} \mid y_i; \theta)
\]

\[
\pi_{ij} = \frac{\pi_j f_j(y_i; \mu_j; \Sigma_j)}{\sum_{j=1}^{k} \pi_j f_j(y_i; \mu_j; \Sigma_j)} \quad j = 1, \ldots, k \quad i = 1, \ldots, n \tag{Eq. 3.5}
\]

\( \pi_{ij} \) is the posterior probability that an individual with observed value \( y_i \) belongs to component \( j \) (for given \( \theta \)).

### 3.5.2.2 The M-step

The M-step maximises \( \ell_C(\theta) \) with \( z_{ij} \) having been replaced by \( \pi_{ij} \). The parameters that maximise \( \ell_C(\theta) \) can be written down explicitly:

\[
\pi_j = \frac{1}{n} \sum_{i=1}^{n} \pi_{ij} \quad j = 1, \ldots, k \tag{Eq. 3.6}
\]

\[
\mu_j = \frac{1}{n \pi_j} \sum_{i=1}^{n} \pi_{ij} y_i \quad j = 1, \ldots, k \tag{Eq. 3.7}
\]

\[
\Sigma_j = \frac{1}{n \pi_j} \sum_{i=1}^{n} \pi_{ij} (y_i - \mu_j)(y_i - \mu_j)^T \quad j = 1, \ldots, k \tag{Eq. 3.8}
\]

These give updated estimates of the parameters \( \theta \) in the iterative procedure.

Equation 3.6 estimates the mixing proportion \( \pi_j \), as the average of the posterior
probabilities $\pi_{ij}$ of all $n$ observations for component $j$. Equations 3.7 and 3.8 calculate the weighted average of the $n$ observations and the weighted sample covariance matrix respectively, both using weights of $\pi_{ij}$.

Before applying the EM algorithm, initial values for the parameters $\theta^{(0)}$ are assigned. The E and M steps are then repeated until some a stopping criterion is met. The stopping criterion is based on the relative change in the log likelihood

$$\ell(\theta^{(k+1)}) - \ell(\theta^{(k)}) \text{ and } (\text{BCEA})^{(k+1)} - (\text{BCEA})^{(k)}$$

at each iteration ($k=1,2,3...$). The program stops when the log likelihood is less than $10^{-4}$ and the BCEA is less than $10^{-3}$. The maximum number of iterations is set at 200. Throughout the E,M process

$$L(\theta^{(k+1)}) \geq L(\theta^{(k)})$$

where $\theta^{(k)}$ are the parameter values after $k$ iterations.

### 3.6 Validation and further information

As these statistical methods have not previously been applied to analyse fixation data, validation of these techniques was performed. This validation will be discussed in the next chapter.
Chapter 4: Validation of novel methods

Two new methods have been introduced in this study - the use of an infra-red eyetracker to measure fixation stability and the statistical techniques described in the previous chapter.

This chapter will justify the selection of these methods and will give results of control experiments performed at the start of this project.

4.1 The use of an infra-red gazetracker to measure fixation stability

Early studies of fixation stability such as those performed by Steinman (Steinman, 1965; Steinman & Cunitz, 1968) used contact-lens based eyetrackers to record eye position and hence fixation stability. However in the last two decades, most fixation stability tests have been administered with either the scanning laser ophthalmoscope or a fundus camera (see section 1.3.1). Where infra-red eyetrackers have been used, these have required rigid head immobilisation (Kosnik et al., 1986; Eizenman et al., 1992).

The SLO has several limitations relevant to the assessment of fixation stability. Stimuli must be monocular, monochromatic images presented at a fixed viewing distance, the subject’s head must be stabilised for satisfactory retinal imaging and in some circumstances pupil dilation is required (Zangwill et al., 1997).

Conversely the infra-red eyetracker can be used with any stimulus, which can be presented in full colour at a wide range of viewing distances under monocular or binocular conditions. The gazetracker used in this study can compensate for head motion so fixation stability can be measured without the need for head immobilisation.

Anecdotally, patients seen in this study appeared to prefer using the eyetracker to the

* This work has been published in Optometry and Vision Science. A reprint of the paper can be found in Appendix 4.
SLO. Although the opinions of subjects were not formally assessed, several patients preferred the free-head nature of the eyetracker and some found it difficult to hear instructions over the noise of the scanning laser ophthalmoscope.

This control study was performed to compare the use of the eyetracker to the SLO in the assessment of fixation stability in subjects with normal vision and those with macular disease.

4.1.1 Methods
Six subjects without macular disease were recruited from colleagues at the Institute of Ophthalmology. All subjects were under 40 years of age and had best corrected visual acuity of 0.1 logMAR or better in both eyes. A further three patients with long-standing AMD were recruited. Patients had an age range of 60-81 years and a VA of 0.3-0.82 logMAR in the tested eye.

4.1.1.1 SLO calibration
In order to quantify the amount of retinal movement from the fundus image produced by the SLO in terms of visual angle, calibration was performed for three of the young subjects. Two of the subjects were emmetropic and one myopic.

A supplementary monitor was used to perform this calibration as target separation could be measured more precisely using this technique. A semi-silvered mirror was placed in front of the SLO so that stimuli produced on a monitor could be viewed on the same visual axis as the SLO. Two targets of known angular separation were presented on the computer monitor and the subject was instructed to alternate fixation between the two points. Simultaneously, fundus images were captured from the SLO. Software designed in-house by E. Dinu tracked retinal landmarks whilst the video was replayed and recorded eye position (in two dimensional pixel coordinates) in relation to the first frame at a frequency of 12.5Hz. The movement of the retinal image between these two fixation positions was calculated for each subject and the distance recorded in image pixels. As the two points on the video monitor are of known angular separation, a simple transformation can describe retinal motion seen on the video image from the SLO in terms of visual angle.
4.1.1.2 Measurement of fixation stability with the SLO
A red fixation cross of height 2.5° was produced in the SLO raster using the SLO’s scotometry module. The subject’s head was restrained with a chin and forehead rest, their left eye was occluded and the right eye was examined. Subjects were asked to fixate the centre of the cross for three separate periods of ten seconds, with timing commencing from apparently stable fixation following a blink. In between each 10 second block, subjects were asked to sit back, blink and then reposition themselves on the SLO. When ten seconds of clear, blink-free data were not obtained, the trial was repeated. Fundus images were recorded continuously throughout the trials on the digital video recorder.

4.1.1.3 SLO data collection
Retrospective analysis of the video tape was made using the software developed in-house with functions supplied with a video board (Orion Frame Grabber, Matrox, Montreal, Canada). This software provides x- and y- axis position of the eye in terms of pixels. The conversion factor found from the calibration stage was used to calculate eye position in terms of degrees of visual angle. A BCEA was produced for each trial using the formula described in section 3.2. The mean of three BCEAs was calculated.

4.1.1.4 Eyetracker calibration
Calibration, drift correction and validation were performed using algorithms supplied by the manufacturers of the gazetracker. Only trials where the calibration was categorised as “good” by the Eyelink software were included. Although the eyetracker can measure both eyes independently and simultaneously, the left eye was again occluded in all trials to ensure similarity of testing in each condition.

4.1.1.5 Measurement of fixation stability with the eyetracker
Fixation stability was recorded using a red cross target of height 2.5° against a dark background. With the exception of the different target, fixation stability was recorded as described in section 2.5.2.2. Patient instruction was identical to that in the SLO condition. Measurements with the eyetracker and SLO were performed in counterbalanced order. Data were cleaned using the Matlab program described in
section 2.5.2.1 and the mean BCEA for three trials was recorded.

### 4.1.2 Results

A strong linear relationship exists between fixation stability measurements made with both instruments for control subjects ($r=0.89$, $n=6$) and for patients ($r=0.99$, $n=3$).

<table>
<thead>
<tr>
<th>Patient initials</th>
<th>Group</th>
<th>Mean SLO BCEA (minarc$^2$)</th>
<th>Mean ET BCEA (minarc$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MC</td>
<td>Control</td>
<td>235</td>
<td>687</td>
</tr>
<tr>
<td>ED</td>
<td>Control</td>
<td>113</td>
<td>526</td>
</tr>
<tr>
<td>PB</td>
<td>Control</td>
<td>331</td>
<td>766</td>
</tr>
<tr>
<td>AC</td>
<td>Control</td>
<td>418</td>
<td>736</td>
</tr>
<tr>
<td>SK</td>
<td>Control</td>
<td>555</td>
<td>892</td>
</tr>
<tr>
<td>GH</td>
<td>Control</td>
<td>623</td>
<td>1272</td>
</tr>
<tr>
<td>RS</td>
<td>Patient</td>
<td>7040</td>
<td>8257</td>
</tr>
<tr>
<td>KD</td>
<td>Patient</td>
<td>823</td>
<td>1023</td>
</tr>
<tr>
<td>MA</td>
<td>Patient</td>
<td>9370</td>
<td>13125</td>
</tr>
</tbody>
</table>

**Table 4.1.** Fixation stability measured for patients and control subjects using the SLO and gazetracker. BCEA: Bivariate contour ellipse area. ET: Eyetracker.

Figure 4.1 displays the results for the subjects without macular disease.

![Figure 4.1](image)

Figure 4.1. Mean BCEA measured by each instrument for the six subjects without AMD. Line fitted using least squares regression. Vertical error bars show ±1 standard deviation. ET: Eyetracker.

BCEAs recorded with the SLO were smaller than those measured by the eyetracker, on average by a factor of 2.13 times.
4.1.3 Discussion
This control study has shown that there is a high correlation between fixation
stability measurements made with our eyetracker and the SLO; individuals who
exhibit poor fixation stability when tested with a scanning laser ophthalmoscope also
have poor fixation stability on the eyetracker.

BCEAs for the eyetracking technique were consistently larger than for the SLO
condition. In the SLO, the patient's head is secured against a chin and forehead rest
and any significant movement of the head interferes with obtaining an image of the
retina. Therefore, data are not recorded during or after head motion. In contrast, the
eyetracker is used without any head support. Although the eyetracker software will
compensate for head movements so that a true gaze position (rather than an eye
position) is recorded, there will still be more retinal motion when a head moves
compared to when it is rigidly fixed due to inefficiency in the vestibulo-ocular reflex
(Steinman et al., 1982; Carpenter, 1988). There are two factors contributing to the
increase in head motion: first, subconscious head tremor would be increased without
the stabilisation of the forehead and chin against the supports on the SLO and
second, subjects are more likely to make small, conscious head movements when it
is unsupported. Further, there is a feedback mechanism to the investigator when
using the SLO: if the retinal image is lost on the SLO display screen due to head
motion then the trial will be discarded and repeated.

The larger BCEAs produced could also be caused by eyetracker errors in the
algorithm used to correct for head movement. Another source of error could be
movement between the eyetracker headband and the forehead of the subject,
although in earlier control experiments we did not find a difference in BCEA when
subjects wore a silicone swimming cap to reduce this slip. The eyetracker software
has more degrees of freedom for measuring eye movement whereas our SLO
program rotational motion could be erroneously recorded as small translational
movements. A previous comparison of the difference in fixation stability between
complete head immobilisation using a dental bite-board and a free-head condition
found an increase of 2-4 times in each dimension (i.e. a 4-16 x increase in BCEA)
(Steinman et al., 1982). The increase of around 2 times BCEA found in the present
study would therefore be expected in a comparison between less rigid head immobilisation (head and chin rest) and the free-head situation.

The sampling rate of the eyetracker is much higher than the SLO. In order to ascertain whether this made any difference to the size of the BCEA, three eyetracker data files were undersampled (by retaining every twentieth line of data but discarding all others) and the BCEA was recalculated. In each instance the BCEA of the undersampled data was comparable to that of the full data set (for full data sets 833, 699 and 1191 minarc², for one twentieth of those data 907, 707 and 1187 minarc² respectively).

A systematic difference has not been found in the repeatability of measurements with each machine. However the relatively high test-retest variability of measurements with both instruments (~20% of the mean value) is a cause of some concern. Large between-trial variability has been noted in similar experiments before; Snodderly and Kurtz even found that subjects' fixation stability improved when a wager involving a milkshake was incorporated into the experimental design (Snodderly & Kurtz, 1985). Artefactual eye position errors can be caused by a number of factors such as blinking, accommodative change (which degrades the quality of the SLO image) and in the case of the eyetracker, wearing mascara or other eye make-up. Careful analysis of data is required to remove frames which display these artefacts before BCEAs are calculated.

A major limitation of the eyetracker is that in patients with scotomas, an eyetracker can only indicate the direction in which the retinal locus for fixation is pointing – not the actual position of the image on the retina. The only way to accurately determine retinal image position is to simultaneously image the retina. At present this is something which is only possible with the scanning laser ophthalmoscope.

4.1.4 Conclusion

Despite the important limitation described in the last paragraph, the eyetracker is a suitable instrument for the measurement of fixation stability in this experiment. The major reasons for the selection of the eyetracker over the SLO are the increased
variety of targets which can be displayed and the fact that fixation stability and other
aspects of visual behaviour can be assessed simultaneously.

The SLO still has a critical role in this study: only with this instrument can the
retinal area or areas used for fixation be determined.

4.2 The kernel density estimator and EM algorithm**

4.2.1 Method
The KDE and EM algorithm described in section 3.3 have been applied to the data
sets of eight patients with macular disease. One (AP) had Stargardt disease and
seven had AMD. Fixation stability assessment was performed as described in
section 2.5.2.1.

A "global" BCEA was calculated in the manner already described. Following this,
the KDE was applied to the data. Where the KDE indicated the existence of
multiple PRLs, the EM algorithm was run to determine the parameters of these
individual loci. The sum of these "local" BCEAs was calculated and compared to
the "global" BCEA.

Repeatability of the techniques was assessed by repeating the analysis on a different
data set from the same patient.

4.2.2 Results
In five patients, the KDE indicated the presence of multiple loci of fixation. In each
of these patients the sum of the local BCEAs was less than the global BCEA, being
on average 58% of the size. Figure 4.2 shows the raw data and kernel plots for these
patients, table 4.2 shows the summarised data from all patients and table 4.3
indicates the properties of the local BCEAs for those patients with multiple PRLs.

** This work has been accepted for publication in Vision Research. A reprint of the paper can be
found in Appendix 4.
Figure 4.2. Data sets and kernel plots for patients (also previous page).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Global BCEA (minarc²)</th>
<th>n PRL</th>
<th>Σlocal BCEAs (minarc²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS</td>
<td>15 900</td>
<td>2</td>
<td>7 950</td>
</tr>
<tr>
<td>KB</td>
<td>3 170</td>
<td>2</td>
<td>2 340</td>
</tr>
<tr>
<td>FG</td>
<td>12 700</td>
<td>3</td>
<td>9 270</td>
</tr>
<tr>
<td>DP</td>
<td>21 700</td>
<td>3</td>
<td>9 240</td>
</tr>
<tr>
<td>TB</td>
<td>1 770</td>
<td>1</td>
<td>1 770</td>
</tr>
<tr>
<td>AP</td>
<td>1 150</td>
<td>1</td>
<td>1 150</td>
</tr>
<tr>
<td>KD</td>
<td>6 340</td>
<td>2</td>
<td>3 260</td>
</tr>
<tr>
<td>HP</td>
<td>2 160</td>
<td>1</td>
<td>2 160</td>
</tr>
</tbody>
</table>

Table 4.2. Summarised data for all eight patients.
M.D. Crossland. Chapter 4: Validation of novel methods.

<table>
<thead>
<tr>
<th>Patient</th>
<th>PRL #</th>
<th>P</th>
<th>BCEA (min arc²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS</td>
<td>1</td>
<td>0.78</td>
<td>5260</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.22</td>
<td>2690</td>
</tr>
<tr>
<td>KB</td>
<td>1</td>
<td>0.50</td>
<td>966</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.47</td>
<td>1370</td>
</tr>
<tr>
<td>FG</td>
<td>1</td>
<td>0.64</td>
<td>2220</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.20</td>
<td>3950</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.16</td>
<td>3100</td>
</tr>
<tr>
<td>DP</td>
<td>1</td>
<td>0.36</td>
<td>2400</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.31</td>
<td>2500</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.22</td>
<td>4340</td>
</tr>
<tr>
<td>KD</td>
<td>1</td>
<td>0.63</td>
<td>2250</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.37</td>
<td>1010</td>
</tr>
</tbody>
</table>

Table 4.3. Parameters of the PRLs for each patient with multiple PRLs. P = proportion of trial for which PRL is being used.

4.2.2.1 Repeatability

For six patients, the analysis was repeated on another fixation trial using the same target and conditions. Unfortunately repeat data were not available for patients DP and AP. Table 4.4 illustrates the repeatability of the technique for the two trials for these five subjects. In one case there are a different number of PRLs elicited: for patient FG there are three PRLs in the first trial and only two in the second. The sum of local BCEAs was found to be similar between the two trials (mean difference = 23%, standard deviation = 7%).

<table>
<thead>
<tr>
<th>Subject</th>
<th>Number of PRLs</th>
<th>Σlocal BCEAs (min arc²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trial 1</td>
<td>Trial 2</td>
</tr>
<tr>
<td>RS</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>KB</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>FG</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>TB</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>KD</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>HP</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 4.4. Comparisons in the number of PRLs and the sum of local BCEAs found for two different trials and applications of the statistical procedure.

4.2.3 Discussion

This control study indicates that the statistical techniques described in chapter 3 are
repeatable in finding the number of PRLs and the sum of the local BCEAs. Many patients display multiple PRLs as defined by this statistical paradigm. Analysis of such patients' fixation data using a global, unimodal BCEA would be inappropriate as the statistical assumption of normality would no longer be valid.

It is perhaps surprising that some of the patients display two or even three loci over a relatively short fixation trial. Other authors have found multiple PRLs only during a complex task such as reading (Duret et al., 1999) or when luminance is changed (Lei & Schuchard, 1997). However these previous studies have only defined PRLs as being separate when they are very well separated, and no quantitative technique was used. The findings of the current study agree with those of Whittaker, who reports that 39% of patients exhibit multiple PRLs (Whittaker et al., 1988).

Unfortunately, as the absolute position of fixation is not known when using the eyetracker, it is not possible to know where the multiple PRLs lie with respect to the lesion. Simultaneous eyetracking and fundus imaging would solve this difficulty. This technique is discussed further in chapters 13 and 14.

4.2.3.1 Limitations of the KDE

The selection of the window width is critical in determining the number of PRLs present. By changing the window width, data can be over- or undersmoothed, giving the impression of more or fewer PRLs being present. An example of changing the window width on one data set is given in figure 4.3. Although the window widths used have been suggested by another group (Bowman & Foster, 1992), further research is required to confirm that this window width is ideal.

For this longitudinal study this limitation is less significant; even if the assessment of the number of PRLs is too conservative or too liberal, changes in the number of PRLs can be observed.
4.2.3.2 Limitations of the EM algorithm

Local maximum problems can cause the loci calculated by the EM algorithm to correspond poorly to the kernel plots in some circumstances. For this reason, the program was run many times on each data set with random start points and the results were always compared to the KDE plots.

A very large PRL used for a very short proportion of the trial was identified in some trials which encompassed all of the other loci. Ad hoc data analysis revealed that the eye was not drifting or fixating at these times but was moving in random direction at a speed below our cut-off velocity for a saccade. Consequently PRLs which are used for <10% of the time have been removed.

4.2.4 Conclusion

The statistical techniques described in chapter 3 are novel and have not previously
been applied to the analysis of fixation. The KDE and EM algorithms give repeatable results within patients at the same visit.
Chapter 5: Characteristics of patients at baseline and results for control subjects

Three analyses are presented in this chapter. First, a profile of the demographic and clinical features of all the patients and control subjects at their initial (baseline) visit to the laboratory is described. Comparisons are made between the patients and the age-matched control subjects, and differences in clinical features between patients with JMD, geographic atrophy and exudative AMD are identified.

The second part of this chapter investigates the performance of control subjects at baseline and at their 12 month visit to determine any improvement which can be attributed to practice or learning effects.

Finally, reading speed characteristics for patients at baseline have been assessed to determine the magnitude of a statistically significant change in reading speed between visits.

5.1 Comparison of patients and control subjects

5.1.1 Specific methods
In general, Student’s t-test has been used to determine differences between groups. However, for some parameters, the variance amongst the patient group is greater than that within the control group. O’Brien’s test can quantify the difference in variance between two populations (Howell, 1997a). When the variances are found to be significantly different then an alternative method is required to analyse differences. In this chapter the Welch test was used to assess significance between groups (Howell, 1997b) where variances were unequal.

5.1.2 Demographic features
Demographic features of patients and control subjects can be seen in table 5.1 below. A full description of each patient can be found in appendix 1.
There was no statistical difference in age between the disease and control group for either older or younger participants (Student’s t-test, older group: \( p=0.79 \); younger group: \( p=0.82 \)).

<table>
<thead>
<tr>
<th>AMD group</th>
<th>Older control group</th>
<th>JMD Group</th>
<th>Younger control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>20</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Mean ±sd age at recruitment (years)</td>
<td>75.2 ±9.3</td>
<td>74.0 ±3.7</td>
<td>29.2 ±12</td>
</tr>
<tr>
<td>Male:female ratio</td>
<td>7:13</td>
<td>2:3</td>
<td>2:3</td>
</tr>
</tbody>
</table>

Table 5.1. Demographic features of patients and control subjects.

5.1.3 Clinical features of AMD patients and older control subjects

The results are described below and are summarised in table 5.2.

Mean distance visual acuity at baseline was 0.66 logMAR for subjects with AMD. This is significantly reduced from the values for the age-matched control subjects (VA for control subjects: 0.05 logMAR; \( p<0.01 \)). Near visual acuity was similarly reduced from N4 in the control group to a mean of N14 in patients (\( p<0.05 \)). In patients, a linear relationship exists between distance and near VA (\( r = 0.77, \ p<0.0001 \)).

Contrast sensitivity was significantly impaired (\( p<0.01 \)), from a mean of 1.60 in normals to 1.15 in patients. Contrast sensitivity was found to correlate with visual acuity in this age-group (\( r = -0.56, \ p<0.01 \)).

Size of the absolute scotomas in the patient group ranged from 0.5 to 5 disc diameters (mean 1.5, sd=1.4). Although there is a trend for patients with larger scotomas to have poorer visual acuity, this relationship does not reach significance (\( r=0.36, \ p>0.1 \)).

Suprathreshold reading speed is reduced in patients, from a mean of 175 words/minute in subjects without macular disease to 82 wpm in those with AMD (\( p<0.0001 \)).
5.1.4 Clinical features of JMD patients and younger control subjects

The patients with JMD also exhibited impaired visual acuity and reading speed when compared to age-matched control subjects. However, contrast sensitivity was not significantly reduced in patients with JMD when compared to the younger control subjects (table 5.3).

Table 5.3. Performance of JMD patients at baseline. * P values calculated by Student's T-test. § F value calculated by Welch test (accounting for heterogeneity of variances). NS: Not significant.

5.1.5 Clinical features and the type of macular disease

Fifteen of the patients in this study (60%) suffer from exudative AMD, five (20%) have geographic atrophy and five (20%) have juvenile macular disease. There are no differences between these three groups of patients in terms of visual acuity (ANOVA, $F_{(df=2, 24)}=0.29$, $p=0.75$), contrast sensitivity ($F_{(df=2, 24)}=0.11$, $p=0.90$) or scotoma size ($F_{(df=2, 24)}=0.73$, $p=0.49$). These data are illustrated in figure 5.1.
Figure 5.1. A comparison of clinical features between the three types of macular disease. Units: Visual acuity: logMAR; Contrast sensitivity: log units; Scotoma size: disc areas.

There is also no difference in suprathreshold reading speed between these three diagnoses (ANOVA, $F_{(df=2, 23)}=0.52$, $p=0.60$).

5.1.6 Discussion
As expected, a significant reduction in performance on clinical tests is found for patients with macular disease. The correlation between visual acuity and contrast sensitivity found in this study ($r = -0.56$) is very similar to previously reported figures from the much larger Salisbury Eye Evaluation study ($n = 2520$, $r = -0.59$, (Rubin et al., 1997)), amongst others (Rubin et al., 1993; Elliott & Situ, 1998; McClure et al., 2000).

There is an over-representation of patients with exudative AMD in this study; only 10% of people with AMD suffer from the exudative form of the disease but more than half of the patients recruited in this study have this diagnosis. One reason for this is the inclusion criterion requiring patients to have experienced a sudden onset of symptoms. This is characteristic of the development of a new lesion in exudative AMD. Those patients with geographic atrophy who were recruited suffered from a sudden increase in scotoma area or a sudden loss of central vision, causing a sudden
drop in visual acuity. It is interesting to note that there are no differences in scotoma size, visual acuity, contrast sensitivity or reading speed between these two groups of patients with AMD.

Younger control subjects displayed better visual acuity and contrast sensitivity than the older control subjects (t-test, $p<0.05$). Age-related decline in visual acuity and contrast sensitivity is well documented (e.g. Rubin et al., 1997). Contrary to previous research (Akutsu et al., 1991), the older control subjects read more slowly than the younger controls ($p<0.05$). The small number of control subjects assessed in this study, particularly in the young group, makes it difficult to draw any firm conclusions from these results.

5.1.7 Summary

Patients with newly presenting macular disease have severely impaired visual acuity, contrast sensitivity and reading speed when compared to age-matched subjects without macular disease. There are no differences in clinical features between patients with wet AMD, dry AMD and juvenile macular disease.

5.2 Change in control subjects' performance over twelve months

To investigate the possibility of a learning effect confounding results found for the patient group, control subjects' performance was assessed twice, with an interval of twelve months between the visits.

5.2.1 Specific method

Data for the young and older control subjects have been pooled for these calculations. A repeated measures analysis of variance has been performed for each variable, to determine any change between the baseline and 12-month visit for any parameter.

A full definition of all of the parameters described in this section can be found in the methods section and the relevant results chapter of this thesis.
5.2.2 Results
As table 5.4 illustrates, there are no significant differences in performance at baseline and at one year amongst the control subjects.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline mean value</th>
<th>One year mean value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual acuity (logMAR)</td>
<td>-0.03</td>
<td>-0.04</td>
<td>0.50</td>
</tr>
<tr>
<td>Contrast sensitivity</td>
<td>1.69</td>
<td>1.72</td>
<td>0.28</td>
</tr>
<tr>
<td>Fixation stability (minarc²)</td>
<td>1,320</td>
<td>1,270</td>
<td>0.82</td>
</tr>
<tr>
<td>Saccadic efficiency (n saccades)</td>
<td>1.75</td>
<td>1.73</td>
<td>0.66</td>
</tr>
<tr>
<td>Saccadic latency (msec)</td>
<td>174</td>
<td>162</td>
<td>0.62</td>
</tr>
<tr>
<td>Peak saccadic velocity (%/sec)</td>
<td>460</td>
<td>501</td>
<td>0.30</td>
</tr>
<tr>
<td>Number of saccades to read a sentence</td>
<td>7.89</td>
<td>7.91</td>
<td>0.95</td>
</tr>
<tr>
<td>Proportion of regressive saccades</td>
<td>7.39%</td>
<td>7.94%</td>
<td>0.62</td>
</tr>
<tr>
<td>Number of saccades to find the start of a line</td>
<td>1.23</td>
<td>1.20</td>
<td>0.57</td>
</tr>
<tr>
<td>Fixation duration (msec)</td>
<td>397</td>
<td>406</td>
<td>0.62</td>
</tr>
<tr>
<td>Reading speed (words/minute)</td>
<td>199</td>
<td>193</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Table 5.4. Differences in performance between baseline and one-year follow-up visit for control subjects.

5.2.3 Discussion
There is no evidence of any training or practice effect between the first visit and an assessment twelve months later in the control subject group. As patients are assessed more frequently than the control subjects there is a chance that some effects of practice may be present which are not apparent by this examination of the control subjects. The design of this study has attempted to minimise the chance of learning effects by providing practice trials at each visit so that patients can refamiliarise themselves with the task and by not repeating charts or text at consecutive visits.

5.3 Determination of a statistically significant change in reading speed

In order to determine a statistically significant change in reading speed, a test for the variability of reading speed within one session is required (Bland & Altman, 1996b; Bland & Altman, 1996a). As the time taken to read at least five suprathreshold sentences (without errors) was recorded at each visit, a measure of the standard
deviation of reading speed can be made for each subject at each visit.

5.3.1 Specific method
The standard deviation of reading speed for each patient was recorded at the baseline assessment. As the size of the standard deviation was proportional to the mean, the coefficient of variability (COV) was calculated for each patient, being (Howell, 1997c):

\[
\text{Coefficient of variability} = \frac{\text{Standard deviation of reading speed}}{\text{Mean reading speed}}
\]

The mean and 95% confidence intervals of the coefficient of variability were calculated and were used to determine the limits for significant changes at later visits.

5.3.2 Results
A strong linear relationship exists between the standard deviation in reading speed and the mean reading speed, with larger values having a larger standard deviation (linear regression; \( r = 0.69, p<0.001 \); figure 5.2). This difference can be eliminated by calculating the coefficient of variability (linear regression against mean reading speed; \( r = 0.17, p=0.50 \); figure 5.3).

The mean COV was 0.14, (95% CI: 0.03 to 0.27). These values are shown on figure 5.3 as a solid horizontal line and two broken horizontal lines.

The upper 95% confidence limit can be used to define clinically significant change between visits (Bland & Altman, 1996b), so an improvement (or deterioration) of 27% in between visits will be determined as significant.
Figure 5.2. Standard deviation of reading speed plotted against mean reading speed at baseline for patients. Line shows linear regression.

Figure 5.3. Coefficient of variability plotted against mean reading speed at baseline for patients. Solid line shows mean value, broken lines 95% confidence interval.
The technique described above makes the assumption that the variance in reading speed at baseline is greater than or equal to the variance subsequently. To ensure that this assumption is correct, the COV in reading speed was calculated at baseline, one month, three months, six months and twelve months for five randomly selected patients. Linear regression indicated a decline in COV at each subsequent visit (r = -0.59, p<0.05). Further, COV did not increase from the baseline value for any subject.
Chapter 6: The location of the PRL and awareness of its use

Section 1.3 of the introduction to this thesis discussed the preferred retinal locus (PRL) and its function in macular disease. The development of the PRL is a major part of the adaptive process of patients with central scotomas. This chapter will assess some aspects of the development of the PRL.

The first section of this chapter discusses the position of the PRL. Previous research based on longitudinal studies has indicated that there is no systematic location for the PRL (e.g. (Sunness et al., 1996; Fletcher & Schuchard, 1997)) and that PRL position is not related to reading speed (Fletcher & Schuchard, 1997). It has been suggested that the location of the PRL will change as patients adapt to their central scotoma. The results in this chapter are the first to assess any change in the PRL location in a longitudinal manner.

The second part of this chapter investigates the point at which patients lose awareness of using the PRL; that is when they report that they are looking directly at a target even when using an eccentric PRL. This adaptation was first described by von Noorden more than 4 decades ago (von Noorden & Mackensen, 1962). More recent work by White and Bedell (1990) and Schuchard (1992) found that this adaptation had been made in 86% and 91% (respectively) of patients with established macular disease. This chapter presents data which describe the length of time which it takes for patients to develop this strategy. The benefit of this adaptation is assessed with respect to suprathreshold reading speed.

This chapter will address two parts of hypothesis 1, which state: “after scotoma development, patients will develop a consistent PRL” and “patients will lose awareness of the use of the PRL”. Hypothesis 4, that reading performance will improve in tandem with the development of adaptive strategies, will also be considered in this chapter.

Raw data for this chapter can be found in appendix 1, under section A1.6.
6.1 The location of the principal PRL

6.1.1 Specific methods
The SLO was used to determine the habitual fixation location when fixating a central cross-shaped target, as described in the methods chapter (section 2.5.1). Briefly, patients are asked to observe a central cross target of 2.5° height presented in the centre of the SLO raster for a period of 30 seconds. All sessions were recorded on digital video.

As subjects without MD use central fixation under all circumstances, control subjects are not considered in this chapter.

6.1.2 Results
6.1.2.1 Location of the principal PRL at baseline
The location of the principal PRL at the baseline assessment for all 25 patients can be found in table 6.1. Five patients displayed central fixation; three of these used a central “island” of residual vision in an area of geographic atrophy and two had juvenile forms of macular disease with paracentral scotomas. Of the 20 patients who used an eccentric PRL, 14 (70%) shifted their fixation horizontally and 6 vertically. PRL location was not dependent on the type of disease: two JMD patients had central fixation, one had a PRL to the left of the scotoma, one had a PRL below and one used a PRL above their scotoma. This distribution of locations is similar to that for AMD patients (table 6.1).

Patients who maintain central fixation have a significantly better visual acuity than those with an eccentric PRL (p<0.01). There are no other relationships between PRL location and visual acuity, contrast sensitivity or scotoma size.

<table>
<thead>
<tr>
<th>Location of principal PRL (in visual field wrt scotoma)</th>
<th>Number (% of patients)</th>
<th>Mean (sd) reading speed (words/minute)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below</td>
<td>3 (12%)</td>
<td>82 (49)</td>
</tr>
<tr>
<td>Left</td>
<td>6 (24%)</td>
<td>91 (36)</td>
</tr>
<tr>
<td>Right</td>
<td>8 (32%)</td>
<td>86 (37)</td>
</tr>
<tr>
<td>Above</td>
<td>3 (12%)</td>
<td>60 (49)</td>
</tr>
<tr>
<td>Central</td>
<td>5 (20%)</td>
<td>74 (50)</td>
</tr>
</tbody>
</table>

Table 6.1. Location of principal PRL at baseline. wrt: with respect to.
Reading speed is approximately equal between the five groups at the baseline assessment (figure 6.1). There are no significant differences between the five PRL locations in terms of reading speed (ANOVA, $F_{(df=4,24)}=0.32$, $p=0.86$).

The theoretically optimum PRL location of placing the PRL below the scotoma in visual field space (described in section 1.3.2.1) was used by three patients at baseline. Patients using this “optimum” PRL location read no faster than those 22 patients using another location (mean “optimum” = 82 words/minute; mean “not optimum” = 81 words/minute, $p>0.9$).

![Figure 6.1](image_url)  

**Figure 6.1.** Mean reading speed at baseline for each patient, grouped by location of the principal PRL. Error bars show 1 standard deviation.

6.1.2.2 *Location of the principal PRL at exit point*

Table 6.2 describes the location of the principal PRL at the exit point from the study.
Table 6.2. Location of principal PRL at exit point from study.

<table>
<thead>
<tr>
<th>Location of principal PRL</th>
<th>Number (%) of patients</th>
<th>Mean (sd) reading speed (words/minute)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below</td>
<td>9 (36%)</td>
<td>75 (27)</td>
</tr>
<tr>
<td>Left</td>
<td>11 (44%)</td>
<td>65 (43)</td>
</tr>
<tr>
<td>Right</td>
<td>5 (25%)</td>
<td>88 (31)</td>
</tr>
<tr>
<td>Above</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Central</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

By the exit point of the study, over half of the patients had changed the location of their principal PRL location. However, there was still no significant difference in reading speed between the three PRL locations (ANOVA, $F_{(df=2,24)}=0.67$, $p=0.52$). Figure 6.2 illustrates the reading speed for each PRL location at exit from the study.

Figure 6.2. Mean reading speed at exit for each patient, grouped by location of principal PRL at exit. Error bars show standard error.

There is no difference in visual acuity, scotoma size or disease type between patients who use a PRL in each of these three locations (ANOVA; VA: $F_{(df=2, 24)}=1.27$, $p=0.30$; Scotoma size: $F_{(df=2, 24)}=0.57$, $p=0.57$; Disease type: $\chi^2=5.79$, $p=0.06$).
6.1.2.3 Change in the location of the PRL

Just over half of the patients changed the location of their principal PRL over the course of the study. All of the patients who initially fixated with a PRL above the scotoma (n=3) or who used a central island for fixation (n=5) changed their fixation location. Three patients changed the location of their principal PRL along the horizontal meridian, from the right to the left of the scotoma. No patients changed their PRL location more than once.

Table 6.3 compares the entrance and exit position of the principal PRL.

<table>
<thead>
<tr>
<th>FROM (PRL location at baseline)</th>
<th>TO (PRL location at 12 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below</td>
<td>Below</td>
</tr>
<tr>
<td>Below</td>
<td>3</td>
</tr>
<tr>
<td>Left</td>
<td>-</td>
</tr>
<tr>
<td>Right</td>
<td>2</td>
</tr>
<tr>
<td>Above</td>
<td>1</td>
</tr>
<tr>
<td>Central</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 6.3. Change in PRL location over the twelve months. Italicised numbers indicate no change. Dashes represent empty fields (for clarity).
Changing PRL location over the course of this study was not related to scotoma size (logistic regression, \( p = 0.14 \)), visual acuity (\( p = 0.33 \)), contrast sensitivity (\( p = 0.64 \)) or whether patients had AMD or JMD (\( \chi^2 \) test, \( p = 0.69 \)).

Although a change in PRL was more likely amongst patients who had a slower reading speed at presentation, this result did not reach significance (\( p > 0.20 \)).

6.1.2.4 Change in PRL location and changes in reading speed

Interestingly, there was no difference in exit reading speed between patients who changed their PRL (mean = 65 words/minute) and those who used the same PRL throughout (mean = 76 words/minute; t-test, \( p = 0.48 \)).

Section 5.3 found a statistically significant change in reading speed to be \( \pm 27\% \) of the baseline reading speed. At the exit point of the study, reading speed had improved by this amount in 5 patients (20%), remained stable in eleven patients (44%) and deteriorated by >27% in 7 patients (28%). Changing PRL location did not predict an improvement in reading speed (\( \chi^2 = 0.25, p = 0.61 \)), or a deterioration in reading speed (\( \chi^2 = 0.20, p = 0.65 \)). The ratio of exit to baseline reading speed was similar in patients who maintained the same PRL (ratio=0.90) and those who changed their PRL (ratio=0.97; Student’s t-test, \( p = 0.69 \)).

6.1.2.5 Time to use the “final” PRL

For the thirteen patients who exhibited a change in PRL location, the point at which the final (exit) PRL was first used was recorded. The median time was 12 weeks (IQR: 8 – 26) and all patients used their exit PRL by the 26 week assessment.

The time to find the exit PRL was not affected by the type of macular disease present (Wilcoxon rank test, \( p > 0.1 \)).

6.1.3 Discussion

The results described above are the first to describe the location of the PRL when macular disease first develops, and to describe the development of the PRL location.

These results indicate that patients make this adaptation surprisingly quickly; half of all patients already used their “final” PRL when they were first assessed, within
three weeks of the development of the scotoma. Amongst those patients who have not started using their final PRL by at the start of the study, the median time to start using their final PRL is only three months. Further, no patients change the location of their principal PRL after their scotoma has been present for six months. Although it is possible that some of these patients will make further adaptations in the years following their scotoma development, the distribution of PRL locations found at exit from this study is very similar to that found in previous cross sectional studies (see section 1.3.2 and table 6.4). These findings indicate that, from the point of view of PRL location, the selection of 12 months as an end point for this study is appropriate.

<table>
<thead>
<tr>
<th>PRL location</th>
<th>Data from this study</th>
<th>Weighted mean of other published studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below</td>
<td>36%</td>
<td>37%</td>
</tr>
<tr>
<td>Left</td>
<td>44%</td>
<td>34%</td>
</tr>
<tr>
<td>Right</td>
<td>20%</td>
<td>18%</td>
</tr>
<tr>
<td>Other</td>
<td>-</td>
<td>11%</td>
</tr>
</tbody>
</table>

Table 6.4. Principal PRL location at exit point from this and published cross-sectional studies.

PRL location does not appear to be associated with reading speed. This corroborates earlier findings from other groups (Sunness et al., 1996; Fletcher et al., 1999). Although half of the patients changed the location of their PRL over the course of this study, this shift did not systematically improve their reading speed.

It has been widely reported that patients rarely use a PRL above their scotoma (Sunness et al., 1996; Fletcher & Schuchard, 1997; Fletcher et al., 1999). All of the patients who used a PRL in this location at the baseline assessment subsequently moved their fixation to a location either below or to one side of the lesion.

All of the patients who initially used a central PRL in an “island” of functioning retina within their lesion switched to another retinal area, presumably one with a larger field of view. These patients did not experience a large drop in VA (as this would have lead to their exclusion from the study), which implies that the same retinal location is likely to have been used throughout for the visual acuity measurements. There is a large size difference between the observed targets for
these two tasks; a 0.5logMAR (~6/12) letter subtends 15 minutes of arc, ten times smaller than the 2.5° cross displayed on the SLO.

Whereas five patients who used a PRL to the right of the scotoma moved their PRL, none of the patients who initially fixated with an area to the left of or below fixation changed their PRL. This reinforces the opinion that using a PRL to the right is less efficient than using a PRL to the left of the scotoma. The reasons for this are unclear, although it must be remembered that only a very small proportion of the time in daily living is spent reading or studying cross-shaped targets. It may be that the use of a PRL to the left of the scotoma is of benefit for locomotion, face recognition or other tasks not assessed here and that some functional benefit is gleaned from this PRL shift.

A methodological problem which affects all research of this type is that the PRL is being assessed during a fixation trial and not whilst patients are reading. It is very difficult to know exactly which retinal area a patient is using when reading conventional text on a SLO as a delay exists between seeing characters in a word and reading the word aloud. This problem is particularly acute when multiple loci of fixation are employed as current methods do not indicate which retinal area a patient is attending to at any given moment.

A further methodological concern is that in the cases of patients with multiple PRLs, the position of a minor PRL may have been recorded as the principal PRL location. This error would lead to a PRL change being described when none existed. The method was applied rigorously to ensure that this was not the case. In practice, as the PRL location was recorded at the end of the microperimetry test (which lasts about 6 minutes) patients routinely fixated with one retinal area. It was the location of this area which was recorded. Further considerations for patients with multiple PRLs will be discussed in the next chapter.

6.1.4 Conclusion
The location of the principal PRL used for fixation does not predict reading speed. This finding reinforces the results of several other research groups. Although half of the patients in the present study changed the location of their principal PRL over the
course of this study, this did not have a significant effect on their reading speed. Patients do not change the location of their principal PRL after six months.

6.2 Awareness of PRL use

6.2.1 Specific methods
After the assessment of the principal PRL, patients were asked to move their eyes to look straight towards the target as described in section 2.5.1.4 of the methods chapter. Briefly, patients were asked to observe the central cross target under these two verbal instructions:

1. “Please look at the red cross in the centre of the screen in front of you”
2. “Please move your eyes so that you are looking straight at the cross, even if it disappears or becomes difficult to see.”

The two instructions were then repeated and the retinal image was digitized under each condition.

As only one retinal image was used for analysis under each instruction, care was taken to ensure that the point selected was within the centre of the locus used under each condition. For the purposes of this experiment, if patients used the same retinal area under each of the instructions then they were said to have pseudofoveated. “Pseudofoveation” and “re-referencing of the oculomotor system” are used as synonyms in this section.

6.2.1.1 Specific statistical methods
Kaplan-Meier survival analysis was performed with pseudofoveation, as described above, being the outcome. Patients who did not pseudofoveate within twelve months were censored.

6.2.2 Results
For one patient (AS) it was impossible to tell whether pseudofoveation had occurred or not; she displayed very unstable fixation under all circumstances. She has therefore been removed from the following analyses.

6.2.2.1 Pseudofoveation and disease type
At the baseline assessment, two of the JMD patients (40%) and two AMD patients (11%) used the same retinal area under both instructions above; that is, they had already pseudofoveated. By the twelve-month follow-up visit, 11 of the AMD patients (58%) and all five JMD patients had pseudofoveated.

The median time to pseudofoveate was 6 months for the AMD patients and one month for the JMD patients. A survival plot, with pseudofoveation as the outcome is shown in figure 6.3. The difference between these groups is highly significant (Wilcoxon rank test, $\chi^2 = 9.4$, $p<0.01$).

All of the patients who pseudofoveated over the course of this study did so by six months. No patients went from having pseudofoveated to a state of non-pseudofoveation.

Figure 6.3. Kaplan-Meier survival plot for AMD and JMD patients, with pseudofoveation as the outcome.

6.2.2.2 Reading speed and pseudofoveation

Patients who have pseudofoveated read more quickly than those who have not. At the exit point, those who have pseudofoveated read at 89 words/minute (sd: 35) whereas those who have not made this adaptation read suprathreshold text at only 58 words/minute (sd: 33). This difference is statistically significant (Student’s t-test, $p<0.05$).
To ensure that this difference was not due to the increased likelihood of pseudofoveation and faster reading speed in the JMD group, the analysis was repeated with stratification by the type of disease. This indicated that the type of disease was not confounding the results.

Of the four patients whose reading speed improved by more than 27%, three (75%) had pseudofoveated, whilst only three of the seven patients whose reading speed deteriorated (43%) made this adaptation.

Reading speed appears to fall in patients who have not pseudofoveated; those without pseudofoveation read at 79% of their baseline reading speed whereas the mean reading speed for those who have pseudofoveated did not change. However, this finding does not reach statistical significance (p>0.05).

6.2.2.3 Prediction of pseudofoveation
Juvenile macular disease patients are more likely to pseudofoveate than patients with AMD ($\chi^2 = 6.3$, p<0.05). There is no association between the likelihood of re-referencing and either visual acuity (logistic regression, p=0.71) or contrast sensitivity at baseline (p=0.22), or scotoma size (p=0.94).

There is no relationship between the PRL location at baseline or at exit and the likelihood of pseudofoveation (logistic regression, baseline, p=0.83; exit, p=0.33). There is also no difference in the likelihood of pseudofoveation between the groups of patients who changed their PRL location (7/12 pseudofoveated) and those who kept the same PRL location (7/12 pseudofoveated).

6.2.3 Discussion
Two-thirds of the patients seen in this study reached a state whereby awareness of using the PRL was lost. This process is quicker and more likely to occur in patients with juvenile forms of macular disease than in AMD patients. All of the five JMD patients seen in this study pseudofoveated, as did all eleven JMD patients in the study by White & Bedell (1990). The first description of pseudofoveation in this way was reported in a patient with JMD (von Noorden & Mackensen, 1962).
Eleven of the nineteen AMD patients (58%) in the present study pseudofoveated within twelve months of scotoma development. This proportion is similar to that found by White and Bedell (7/10 AMD patients). The time since onset of scotoma in White’s study ranged from 1 to 17 years so it appears that some patients never make this adaptation. The similarity in the proportion of patients who pseudofoveate between these studies makes it tempting to speculate that the patients who have not made the adaptation by the exit point from this study are not likely to develop this strategy of re-referencing their oculomotor system to the PRL in the future. Whether training or any other intervention could encourage these patients to pseudofoveate is beyond the scope of this thesis but will be discussed in the general discussion chapter of this thesis.

Some patients had already developed a state of pseudofoveation at the baseline assessment, within three weeks of scotoma development. There are no differences evident between these patients and those who did not develop pseudofoveation so quickly. If it were possible to assess patients with a shorter interval between vision loss and baseline assessment, the point at which these four patients developed pseudofoveation could be defined. Unfortunately, due to issues of informed consent, medical retina assessment and laboratory time, this was not possible in the current study.

Suprathreshold reading speed is faster in those patients who have pseudofoveated, regardless of PRL location. Reading speed appears to be more likely to deteriorate in patients who have not made this adaptation. This finding has relevance for the development of training programmes for patients with macular disease; if patients are encouraged to use an alternate retinal location (rather than the location which is naturally chosen), awareness of PRL use would be greater. This would decrease the likelihood of pseudofoveation and may be counterproductive. The development of training programmes is discussed in chapter 14.

The most likely reason for the difference in reading speed in patients who have re-referenced is that the saccades of patients who have pseudofoveated will be guided to the PRL rather than to the scotoma. This hypothesis will be investigated further later in the thesis.
Encouragingly, pseudofoveation does not appear to be dependent upon factors such as visual acuity, scotoma size or reading speed at presentation. These results indicate that even patients with very large scotomas (with dense scotoma of up of five disc diameters area) may re-reference their oculomotor system to an eccentric locus over time. Patient symptoms were not recorded during this study, therefore it is not possible to know whether patients’ subjective performance is related to pseudofoveation.

It is not clear from the these results whether pseudofoveation itself increases reading speed or whether other factors which improve reading, such as modified saccade control, in turn lead to re-referencing of the oculomotor system. The interaction of all of the factors investigated in this thesis will be described in chapter 10.

For the present study, pseudofoveation has been defined as the stage at which patients do not have awareness of the use of their PRL under monocular conditions. However it is not clear whether this is an indication of complete re-referencing of the oculomotor system. Performing an orthoptic test such as a cover test would indicate whether the PRL is behaving as the centre of the oculomotor system in other respects.

### 6.3 Summary of chapter 6

The key finding of this chapter is the discovery of the time it takes for patients to develop their “final” PRL. Although several studies have suggested that PRL development takes time, this project is the first to quantify how quickly the PRL develops. The results in this chapter show that although some patients use the same PRL from when their scotoma first develops, half of all patients subsequently adopt a new location for their principal PRL. On average, this adaptation takes three months and all patients adopt their final PRL within six months of scotoma development. Changing the PRL does not appear to be beneficial in terms of reading speed improvement.

No association is found between reading speed and the position of the principal
PRL. Although this finding may be intuitively surprising, it confirms previous research by other groups.

This chapter has also discussed the phenomenon of pseudofoveation; that is, the lack of awareness of PRL use. The results found in this experiment indicate that patients who have no awareness of using a PRL read more quickly than those who are conscious of not looking straight ahead when they are using their PRL. These findings provide some reinforcement for the suggestion of White and Bedell (1990) that, with time, some patients "(show) oculomotor behaviours qualitatively more like those of normals, although centred about a nonfoveal locus."

This chapter supports the parts of hypothesis 1 which state that "after scotoma development, patients will develop a consistent preferred retinal locus" and that in many cases "patients will lose awareness of the use of the PRL."

Further aspects of the PRL are fixation stability and the number of PRLs used. These phenomena will be examined in the next chapter.
Chapter 7: Fixation stability and the number of preferred retinal loci

Chapter 6 examined the development of the PRL in terms of its location and awareness of its use. The first part of this chapter will investigate the stability of fixation within this PRL and will relate fixation stability to reading speed. The second part of this chapter will examine patients with multiple PRLs.

7.1 Fixation stability

7.1.1 Specific methods
Fixation stability was assessed using the infrared eyetracker as described in section 2.5.2.2 and a BCEA was calculated for each target location using the formulae given in chapter 3. Where multiple PRLs were determined by the KDE, the sum of local BCEAs was calculated and recorded as fixation stability. The mean BCEA (or mean sum of local BCEAs) for all locations was recorded and used for the analyses in this chapter.

7.1.2 Results
All of the data used for this analysis can be found in section A1.7, appendix 1.

7.1.2.1 Fixation stability
As BCEA values for patients were not normally distributed (Shapiro-Wilk test, W=0.53, p<0.001), a natural log transform was performed to normalise them (W=0.99, p=0.98).

The mean BCEA for control subjects was 1,614 minarc² at baseline (sd=1,022) and 1,270 minarc² (sd=574) at twelve months. For patients, mean logBCEA at baseline was 9.04 log units (sd=1.16), and 9.00 log units at the exit from the study (sd=1.44). These log values correspond to 8,433 and 8,103 minarc² respectively. These values are far poorer than those for control subjects (Student’s t-test, p<0.001 at entrance and exit).
In patients, the size of the BCEA was not associated with visual acuity (at baseline, $r = 0.38$, $p = 0.1$; at exit, $r = 0.36$, $p = 0.1$), contrast sensitivity (baseline $r = -0.09$, $p = 0.62$; exit $r = -0.10$, $p = 0.74$) or scotoma size (baseline $r = 0.13$, $p = 0.54$; exit $r = 0.20$, $p = 0.38$). Although patients with JMD showed more precise fixation than those with age-related forms of macular disease, this finding did not reach significance (Mean (sd) BCEA: JMD patients: $8.54 \log \text{min} \text{arc}^2$ (1.23); AMD patients: $9.19 \log \text{min} \text{arc}^2$ (0.73); $p = 0.14$). In patients with AMD, the type of disease was not related to fixation stability ($p = 0.56$).

### 7.1.2.2 Change in fixation stability

There is not a significant difference between fixation stability at entrance and exit for patients ($p = 0.69$) or for control subjects ($p = 0.40$). Figure 7.1 illustrates the lack of a systematic change in fixation stability in patients and control subjects.

![Figure 7.1](image)

**Figure 7.1.** Fixation stability at entrance and exit. Control subjects shown as open boxes, patients as filled circles. Line shows $y=x$. $n=30$.

Improvement in fixation stability was defined by subtracting $\log \text{BCEA}_\text{exit}$ from $\log \text{BCEA}_\text{baseline}$ (i.e. calculating the ratio of fixation stability at exit to that at baseline, with positive values corresponding to an improvement in fixation stability). The mean change in fixation stability was $-0.07$ (sd: 0.93). This indicates that, on
average, fixation stability decreased by 7% over the course of the study. The large standard deviation indicates that there is no systematic change in fixation stability. This can be confirmed by visual inspection of figure 7.1; fixation stability improves and deteriorates in a similar number of patients.

There was no difference in the magnitude of change in fixation stability between patients with geographic atrophy (mean change -0.04), exudative AMD (mean change -0.15) and those with juvenile macular disease (mean change 0.13; between pairs t-test, p>0.05).

7.1.2.3 Reading speed and fixation stability
For control subjects, a negative correlation was found between BCEA and reading speed at baseline assessment (r = -0.66, p<0.05). This indicates that control subjects with poorer fixation stability read more slowly than those with smaller BCEAs. In patients, there was a similar association between reading speed and BCEA at the baseline assessment (linear regression, r = -0.46, p<0.05; figure 7.2). This correlation was maintained at subsequent visits; at the exit point of the study the correlation coefficient between fixation stability and reading speed was -0.51 (p<0.05).

![Figure 7.2.](image)

**Figure 7.2.** Reading speed and fixation stability for all patients at baseline. Line shows linear regression. n=24 (excludes AP).
7.1.3 Discussion

Fixation stability is significantly impaired in patients with macular disease. This reinforces the findings of previous research (Culham et al., 1993; Schuchard & Fletcher, 1994; Rohrschneider et al., 1995). The level of this impairment in stability is not related to the type of disease present, visual acuity, contrast sensitivity or scotoma size. The observation of a very large inter-patient difference in the size of the BCEA has been made previously by Culham, Fitzke, Timberlake and Marshall (Culham et al., 1993).

It is perhaps surprising that there is no relationship between scotoma size and fixation stability, as fixation is known to be less precise as eccentricity increases (Sansbury et al., 1973), and a larger scotoma will lead to a more eccentric PRL being used. However, this lack of correlation has been reported previously (Timberlake et al., 1986; White & Bedell, 1990).

This is the first study to have examined the change in fixation stability immediately after the development of a scotoma. These results do not show any systematic change in fixation stability over the first twelve months after the onset of macular disease in the second affected eye. In a cross-sectional study, White and Bedell did not find a significant correlation between duration of disease and fixation stability (White & Bedell, 1990).

In subjects without macular disease, fixation stability is related to suprathreshold reading speed. Research on patients with impaired reading due to dyslexia has suggested that fixation stability is a corollary of reading speed (see e.g. (Eden et al., 1994)) and these results reinforce the opinion that more precise fixation stability is associated with better reading ability.

In the presence of macular disease there is a weaker relationship between reading ability and fixation stability. Although in a review paper Schuchard has suggested that more stable fixation may be beneficial (Schuchard & Fletcher, 1994), the results in this thesis constitute the first evidence of a correlation between fixation stability and reading rate.
7.1.4 Conclusion
Fixation stability is significantly impaired in subjects with macular disease. Fixation stability does not consistently improve over the first twelve months after developing a scotoma. Fixation stability is related to reading speed at both the entrance and the exit point from the study.

The results presented in this section do not support the part of hypothesis 1 which states “…fixation stability will improve.”

7.2 The number of preferred retinal loci

7.2.1 Specific methods
Fixation was recorded in the manner described above and data were retrospectively assessed by the KDE, as described in chapter 3. The number of PRLs evident on each fixation trial was calculated, and the mean number of PRLs for 5 fixation trials was recorded. It was also noted whether patients used the same number of PRLs for targets in any of the five positions of gaze, or a variable number of PRLs depending on where the target was located.

7.2.2 Results
7.2.2.1 Multiple PRLs at baseline
Seven patients (28%) use more than one PRL when fixating a central target at the baseline assessment, although a further nine patients use multiple PRLs when viewing at least one of the non-centrally presented targets. Of the 16 patients who use more than one PRL, the mean number of PRLs used for the five screen positions was 1.7 (range 1.2 – 3.8).

There is no difference between the patients who use one PRL under all circumstances and those who exhibit multiple PRLs in terms of visual acuity (Student’s t-test, p=0.13), contrast sensitivity (p=0.60), scotoma size (p=0.97) or disease type ($\chi^2=0.18$, p=0.67). Patients with multiple PRLs tend to have poorer fixation stability than those who used only one locus of fixation but this result does
not reach statistical significance (Student’s t-test, p=0.08).

7.2.2.2 Change in the number of PRLs used

Over the timescale of this study, 11 patients (69% of those with multiple PRLs) displayed a reduction in the mean number of PRLs used. Eight of the patients who initially used multiple PRLs used only one PRL at the exit point of the study. Three of the 16 patients with multiple loci at baseline used the same number of PRLs at each visit. In five patients there was an increase in the number of PRLs used. These findings are summarised in table 7.1 below.

<table>
<thead>
<tr>
<th>Single PRL at baseline</th>
<th>Multiple PRLs at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change</td>
<td>↑ n PRL</td>
</tr>
<tr>
<td>AP</td>
<td>DB (1 - 2)</td>
</tr>
<tr>
<td>CA</td>
<td>EC (1 - 2)</td>
</tr>
<tr>
<td>JE</td>
<td>RS (1 - 1.7)</td>
</tr>
<tr>
<td>JY</td>
<td></td>
</tr>
<tr>
<td>KD</td>
<td></td>
</tr>
<tr>
<td>SG</td>
<td></td>
</tr>
<tr>
<td>JA</td>
<td></td>
</tr>
<tr>
<td>MF</td>
<td></td>
</tr>
</tbody>
</table>

Table 7.1. Change in the number of PRLs used by patients. nPRL = number of PRLs used. ↑=increase. ↓=decrease. Letters are patient initials. Numbers in parentheses indicate the number of PRLs used at entrance and exit (respectively).

There is an increase in the number of patients using one PRL during this study, from 9 at baseline (36%) to 14 (56%) at exit. A more pronounced increase is seen in the proportion of patients using a repeatable number of PRLs (be it one or two) for all fixation positions, from 12/25 patients at baseline (48%) to 19/25 (76%) at exit. These results can be seen in figure 7.3.
7.2.2.3 Reading speed and the presence of multiple PRLs

Patients who exhibit one PRL read significantly faster than those who display multiple PRLs at baseline (Student’s t-test, p<0.05). Amongst those who use multiple PRLs, there is no significant difference in reading speed at baseline between those who use a repeatable number of PRLs and those who do not (t-test, p=0.81). These results can be seen graphically in figure 7.4.

At the exit point from the study, patients with multiple PRLs read at a similar rate to those with one PRL (p=0.36). Patients who used the same number of PRLs for each condition read significantly faster than those who had a variable number of PRLs (Student’s t-test, p<0.05). There is no difference in reading speed between those who displayed one PRL at exit and those who consistently used two PRLs (Student’s t-test, p=0.80). These data are illustrated in figure 7.5.
Figure 7.4. Reading speed and the number of preferred retinal loci at baseline. nPRL: number of PRLs. Error bars show 1 standard deviation.

Figure 7.5. Reading speed and number of PRLs used at exit point from the study. Error bars show one standard deviation.
Patients can be grouped into those who change the number of PRLs which are used and those who use the same number throughout. Comparing these groups reveals no difference in the improvement in reading speed (Student's t-test, p=0.80). Subgroup analysis of those patients who reduce the number of PRLs from many to one indicates that their reading speed does not improve any more than patients who do not make this “optimum” adaptation (p=0.20).

7.2.2.4 Time to develop the optimal number of PRLs
By the end of this study, 19 patients used a repeatable number of PRLs, either one or two. If the assumption is made that this is the optimal situation, the end-point of a patient’s adaptation, then the time taken to reach this state can be recorded for these nineteen patients. These times are illustrated in table 7.2 below.

<table>
<thead>
<tr>
<th>Time to use a non-variable number of PRLs</th>
<th>Number (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>1 month</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>3 months</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>6 months</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>12 months</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Always use a variable nPRL</td>
<td>6 (24%)</td>
</tr>
</tbody>
</table>

Table 7.2. Time to use a non-variable number of PRLs.

There is no difference in scotoma size between the patients who use exactly one and exactly two PRLs at exit (p=0.99). All of the patients with JMD used only one PRL.

7.2.3 Discussion
Hypothesis 1 of this thesis states that “the number of different PRLs used will reduce from many to one”. This does not appear to be the case; at the exit point of this study more than one in three of the patients exhibited multiple PRLs. Of these eleven patients, five reliably used two PRLs for observing the target, regardless of the position of gaze.

Initially it seems surprising that multiple PRLs were used by some patients for a simple fixation task as previous researchers have only elicited multiple PRLs when
patients have observed a target of variable size (Guez et al., 1993) or luminance (Lei & Schuchard, 1997). However, the target used in this experiment was a large black circle with a smaller (18') central detail (described in section 2.5.2.2 and illustrated in figure 7.6). Patients may use one PRL to find the location of the black circle on the screen and then a second PRL with better visual acuity to examine the central detail. As reported in chapter 6, all of these patients had an identifiable "principal" PRL which could indicate that the secondary PRL was used for localisation of the target, whilst the principal PRL was used for detailed target examination.

Unfortunately from the eyetracker data collected it is not possible to determine the strategies which patients used to switch between their PRLs.

![Figure 7.6. Target used for identification of multiple PRLs.](image)

The statistical technique to identify multiple PRLs used in this thesis is more sensitive than that used in other research. This may cause a higher incidence of multiple PRLs to be reported.

Whittaker suggested that patients with larger scotomas (>20°) were more likely to display multiple PRLs (Whittaker et al., 1988). The three patients in this study with scotomas of this size or greater (RH, BP and JW) all displayed multiple loci at exit. However the mean scotoma size was not significantly different between the group using one PRL and those using multiple PRLs (p=0.29).

As elsewhere in this thesis, an assumption is made that the performance of patients on a fixation task can be correlated to their performance on a reading task. It is very difficult to assess how many PRLs are being used when reading as it is unclear which retinal area a patient is attending to at any given time when the eye is moving along a line of text. An experimental technique which may address this concern is
suggested in chapter 13. Not all patients have developed a repeatable number of PRLs by the exit point of this study, as can be seen in figure 7.3. The median time to develop a repeatable number of PRLs is 1 month, although 6 patients do not make this adaptation within twelve months. Longer follow-up would determine whether all patients eventually develop a strategy whereby one (or two) PRLs are used routinely or whether some patients never make this adaptation. All of the patients who do not use a repeatable PRL suffer from AMD.

There is no evidence to suggest that those patients who consistently use two PRLs will change to using one PRL. Large cross-sectional studies have found a similar incidence of multiple PRLs as this study (e.g. 39% in the study by Whittaker (1988), compared with 44% in the present study). A longer period of follow-up would confirm this impression that many patients may continue to use two PRLs.

7.2.4 Conclusion

Over time, some patients develop a strategy whereby the same number of PRLs are used for examining targets in any location. Patients with this strategy read more quickly than those who do not use the same number of PRLs under all conditions. The time taken to make this adaptation is variable and may exceed twelve months. A significant proportion of patients repeatably use two PRLs for observing a target. There is no difference in reading speed between patients who use one PRL and those who consistently use two PRLs. The results of this section indicate that the presence of multiple PRLs does not impair reading speed, as long as patients display a consistent strategy for using these PRLs.

7.3 Summary of chapter 7

Fixation stability is significantly impaired in patients with macular disease but is not related to visual acuity, contrast sensitivity, scotoma size or type of disease. There is no consistent change in fixation stability over the course of this study.

Many patients display multiple PRLs when observing a point target. Using two
PRLs does not appear to affect reading speed, as long as patients display a consistent strategy for using these PRLs.

The section of hypothesis 1 which states "the number of different PRLs used will reduce from many to one and fixation stability will improve" has not been supported.
Chapter 8: Saccadic considerations

This chapter will assess eye movements when subjects are observing a moving target. Saccades made by patients with central scotomas are interesting for several reasons.

First, the number of saccades used to perform a task is a measure of how efficiently the saccadic system is being used. McMahon and colleagues have shown that the number of excessive saccades used by a patient for a specific task can predict a reduction in performance on a reading task (McMahon et al., 1991; McMahon et al., 1993). The number of saccades used can also indicate the extent to which the oculomotor system has been re-referenced; a larger number of saccades suggests that patients are making a saccade to the scotoma before using the PRL (White & Bedell, 1990) or that patients can not reliably “find” their PRL (Schuchard et al., 1999).

Second, the latency and velocity of saccades can determine whether patients are using a foveating or non-foveating mechanism for guiding their saccades. Foveating saccades are distinguishable from non-foveating saccades of the same magnitude due to their shorter latency and higher peak velocity (section 1.4.1, (Whittaker & Cummings, 1990b; Whittaker et al., 1991)). Patients with bilateral scotomas must rely on non-foveating eye movements. The suppression of foveating eye movements and the development of a non-foveating saccade mechanism is a key part of patients’ rehabilitation.

The results in this chapter have been divided into three sections (8.2 to 8.4). First, the relationship between the latency, velocity and number of saccades is assessed, and differences between horizontal and vertical saccades are described. The second section addresses the number of saccades used to perform a task (saccadic efficiency). Section 8.4 examines the latency and velocity of saccades with reference to whether a foveating or non-foveating system is being employed.

This chapter will address the part of hypothesis 2 which state that “the number of
saccades used to locate a target will reduce over time. Foveating saccades will be suppressed and eye movements will be made directly to the PRL rather than to the scotoma.”

8.1 Specific methods

Saccadic latency, efficiency and velocity were recorded whilst observing a moving target as described in section 2.5.2. Briefly, after calibration and drift correction, the Eyelink gazetracker was used to record eye movements as patients followed a jumping target of 3° diameter with an 18' central detail. In the first experiment, the target moved from the centre of the screen to a randomly selected location either 18° to the left or to the right of the original position. In the second experiment, the target decentration was 12° above or below the centre. In both cases the target appeared immediately when the previous target disappeared, and the target moved every 5 seconds. In between each presentation, the target returned to the central position for 5 seconds. There were 20 eccentric target presentations per experiment and only saccades away from the centre were analysed, not those made to the target when it was located in the centre of the screen.

Retrospective analysis of the data recorded by the gazetracker was performed. In each case, the saccadic latency, number of saccades to find the target (saccadic efficiency) and peak velocity were recorded. The mean values for all 20 trials were calculated.

Full data can be found in appendix 1, section A1.8.

8.2 Interaction between saccadic properties in each meridian

8.2.1 Relationships among saccadic efficiency, latency and velocity

To determine the independence of saccadic efficiency, latency and velocity, a correlation matrix was constructed to assess association between these variables for all patients at their baseline visit. Spearman’s test was used to assess the correlation between each parameter. Spearman’s test is a non-parametric measure of association between variables. Data are placed into rank order and the correlation coefficient $\rho$
is computed using Pearson’s product-moment correlation formula. A nonparametric
test is required as saccadic latency is affected by age (Whitaker et al., 1986; Pitt &
Rawles, 1988). Only data for the horizontal dimension has been included in this
analysis. The correlation matrix can be seen in Figure 8.1. There are no significant
correlations between these variables when Spearman’s test is applied (see table 8.1.).

| Variable 1              | Variable 2              | Spearman $\rho$ | $p > |\rho|$ |
|-------------------------|-------------------------|-----------------|-------------|
| Saccadic efficiency     | Saccadic latency        | 0.124           | 0.55        |
| Saccadic velocity       | Saccadic latency        | 0.157           | 0.47        |
| Saccadic velocity       | Saccadic efficiency     | -0.251          | 0.24        |

Table 8.1. Spearman’s rho coefficients between saccadic latency, efficiency and mean peak velocity in the horizontal dimension at baseline assessment for all patients.

Figure 8.1. Scatterplot matrix to compare saccadic latency, efficiency and mean peak velocity in the horizontal dimension at baseline for all patients. Ellipses show 95% confidence intervals. $n=25$. 
8.2.2 Systematic differences in saccades made in different directions

8.2.2.1 Saccadic latency

As there is known to be an age-related change in saccadic latency and the distribution of age in this study is bimodal rather than normal, AMD and JMD patients are considered separately in this analysis.

Saccadic latency is not significantly different in any of the four directions of gaze (repeated measures ANOVA, AMD patients: p=0.45, figure 8.2; JMD patients: p=0.71). Further analysis of saccadic latency data for all patients and control subjects indicates that no difference exists between the latency of horizontal saccades and of those in the vertical direction (Spearman’s test, ρ=0.67, p<0.001).

![Figure 8.2. Latency for saccades in different directions. Error bars show 1 standard deviation.](image)

The location of the scotoma with respect to fixation is known from the scanning laser ophthalmoscopy performed at each visit. When those saccades which are made towards the scotoma are compared to saccades in the opposite direction, no difference in latency is found (Student’s t-test, p=0.39).
8.2.2.2 Peak saccade velocity

In a similar fashion to saccadic latency, there is no systematic difference in peak velocity for patients in the four directions of gaze (repeated measures ANOVA, p=0.79; figure 8.3). Saccades made towards the scotoma are no slower than those made in the opposite direction (Student's t-test, p=0.81).

![Figure 8.3. Peak velocity for saccades in different directions. Error bars show 1 standard deviation.](image)

8.2.2.3 Number of saccades to find a target

There is no difference in efficiency between the four saccade directions for patients (repeated measures ANOVA, p=0.63; figure 8.4). For control subjects, significantly more saccades are made to observe a target presented above fixation (p<0.05), but no differences in saccade accuracy exist between the other three positions of gaze.

The same number of saccades are made to observe a target displaced in the direction of the scotoma as to view a target displaced in the opposite direction (Student's t-test, p=0.72).
8.2.3 Discussion

This section has shown that saccadic latency, accuracy and efficiency are not systematically different in the horizontal and vertical dimensions. Although no differences between horizontal and vertical saccades have been previously reported in healthy subjects (Balliet & Nakayama, 1978; Carpenter, 1988; Kubo et al., 1991), this is the first such comparison in patients with macular disease.

No significant association has been found between saccadic latency, accuracy and efficiency. These parameters will be examined separately below.

8.3 Saccadic efficiency: the number of saccades used to view a target

When a normally sighted observer fixates a target which is decentred by more than 10°, more than one eye movement is made (Dodge & Cline, 1901; Carpenter, 1988). The first, hypometric saccade covers about 90% of the distance towards the target.
and a second, correcting saccade brings the object onto the fovea. As the horizontal target decentration in this experiment is 18°, it would be expected that more than one saccade be used by patients and control subjects. However, to use three or more saccades would be abnormal (White & Bedell, 1990).

McMahon and colleagues examined the number of saccades used when patients were asked to look at each of five letter targets in turn (McMahon et al., 1991). They found that the number of saccades used was doubled in patients with AMD when compared to control subjects.

White (1990) suggested that saccades made to the scotoma were less prevalent in patients with very long-standing macular disease, and so fewer saccades were made to observe a target by her patients. This impairment in the ability to make saccades to the PRL in patients with macular disease has also been described by Schuchard and coworkers (Schuchard et al., 1999).

This section will analyse the number of saccades used to observe a target in patients with macular disease when compared to age-matched control subjects. It will also address the hypothesis made above that with time, the number of saccades made to observe a target will fall.

8.3.1 The effect of macular disease on saccade efficiency

The mean number of saccades used by patients to observe a target ranged from 1.3 to 4.2 saccades (mean=2.1, sd=0.7), whilst all control subjects found the target with less than two saccades (range 1.25-1.95, mean=1.7, sd=0.24). There is a significant increase in the number of saccades made by patients (Welch test, F(df=1, 32) =5.72, p<0.05).

Post-hoc analysis shows that patients with juvenile macular disease make more saccades than those with AMD (Tukey-Kramer HSD, p<0.05), although there was no age-related difference in the number of saccades used by control subjects. Patients with geographic atrophy make the same number of saccades as those with exudative AMD.
8.3.2 Saccade efficiency and reading speed

There is a strong relationship between the number of saccades used to read a sentence and suprathreshold reading speed in patients at the baseline assessment \( r = -0.62, p<0.01 \); figure 8.5). This relationship, including interactions with other factors, will be assessed in detail in chapter 10 of this thesis.

![Figure 8.5. Saccadic efficiency and reading speed for all patients at baseline. n=24 (excludes AP).](image)

8.3.3 Changes in saccade efficiency with time

Control subjects’ saccade efficiency remains constant throughout this study (section 5.2.2). As figure 8.6 shows, the mean number of saccades used by patients also remains constant at around 2.2 saccades. A repeated measures analysis of variance was performed to determine whether differences in saccadic efficiency occurred over time. No statistically significant differences were found over the 12 months of this study (repeated measures ANOVA, 0-12 months, \( p=0.23 \)). As the repeated measures ANOVA excludes all patients with any missing data and some patients were excluded from the study before their 12 month visit, the ANOVA was repeated to compare performance at 0 and 6 months. Although this analysis had more subjects, no change was found between these visits (repeated measures ANOVA, 0-6 months, \( p=0.24 \)).
Although the mean value for the number of saccades used remained constant throughout the follow-up period of this study, in individual cases the number of saccades used changes markedly. For example, in patient BP the number fell from 2.95 to 2.15 and in patient EC the number of saccades rose from 1.35 to 2.05. Figure 8.7 shows individual changes in saccadic efficiency.

**Figure 8.6.** Change in saccade efficiency for patients (filled symbols) and control subjects (open symbols). Error bars show one standard deviation.
Figure 8.7. Change in saccade efficiency between baseline and exit for individual AMD patients. Red lines show a decrease in the number of saccades used. n=20 (computational limitations).

8.3.4 Discussion

This section has found that saccadic efficiency is impaired in patients with macular disease throughout this study. There are two possible explanations for this; first, patients are making erroneous foveating saccades to the scotoma before making correcting eye movements to the PRL. Second, patients may be directing their saccades directly to the PRL but these saccades are less accurate than those made to the fovea by individuals without macular disease.

Unfortunately, as the retina was not imaged during these experiments, it is not possible to know which of these explanations is correct. In a similar task, Whittaker found that only one patient of 18 made saccades to the scotoma rather than to the PRL (Whittaker et al., 1991). However, this one patient had the shortest history of macular disease (1 year).

To observe the target with less than two saccades indicates that patients must be guiding their saccades directly to the PRL rather than making foveating saccades. It can be seen from figure 8.5 that these patients read more quickly than those with
worse saccade efficiency.

There is no systematic change in the number of saccades used to observe a target over the course of this study. However, large changes in the number of saccades used were observed in some individuals. By the exit point of the study, eight patients reliably observed the target with two saccades or less: patients BN, IP, JE, JF, JM, KD, PF and RH. There is no difference between these patients and the remaining 17 patients in terms of visual acuity (p=0.43), scotoma size (p=0.99) or disease type (p=0.52).

To determine whether these patients may be those who have fully re-referenced their oculomotor system and will have pseudofoveated, in the manner described in chapter 6, a logistic regression model was constructed for all patients at their exit point from the study. This model determined whether the number of saccades used to view a target could predict the likelihood of pseudofoveation. It was found that there was no relationship between the number of saccades used to view the target and pseudofoveation at the exit point ($\chi^2=0.12$, p=0.72).

None of the patients in the present study received any training or other intervention. McMahon and colleagues found that with saccadic training, the number of saccades used to view a target fell, although it did not reach normal values (McMahon et al, 1993). Encouragingly, there was a concurrent improvement in reading speed in these patients. It is tempting to speculate that with training, the saccadic efficiency of patients in the present study can be improved. A potential training system is discussed in chapter 14.

8.3.5 Conclusion

Throughout this study, patients with macular disease make more saccades to observe a target than do age-matched control subjects. Although there is no systematic change in saccade efficiency, some patients demonstrate a marked increase or decrease in the number of saccades used to fixate a target. This change does not appear to be related to the development of pseudofoveation.

Chapter 11 will investigate the relationship between changes in saccadic efficiency
and changes in reading speed.

8.4 Saccadic latency and velocity

This section will examine the saccadic latency and velocity of the patients and will compare these values to those of the age-matched control subjects. The motivation for this section is to determine whether patients are using foveating or non-foveating eye movements, as described by Whittaker (Whittaker & Cummings, 1990a; Whittaker & Cummings, 1990b).

Saccadic latency in young subjects without macular disease is around 120 msec (Carpenter, 1988; Pitt & Rawles, 1988). Saccadic latency increases by 1 to 2 msec/year over the age of 20 (Abel et al., 1983; Carter et al., 1983; Whitaker et al., 1986; Pitt & Rawles, 1988). Whittaker and colleagues found saccadic latency to be increased to 402 msec in patients from a mean value of 298 msec in control subjects (Whittaker et al., 1991). Although the control subjects in Whittaker's study were not exactly age-matched, the differences in age were not sufficiently large enough to account for this large difference in latency. White & Bedell also found saccadic latency to be increased in all but one of their AMD patients when compared to age-matched control subjects (White & Bedell, 1990).

Saccade velocity also slows with age, although this change is less pronounced than that in saccadic latency (Pitt & Rawles, 1988). Whittaker found the peak velocity of saccades in patients with macular disease to be somewhat reduced, although he did not quantify this difference in speed (Whittaker et al., 1991). No other research groups have reported the speed of saccades in macular disease.

Examination of the latency and speed of patients' saccades can determine the mechanism which patients are using to make eye movements; if the latency and velocity is the same as that for age-matched control subjects then the foveating saccade mechanism is being used. However if the velocity is slower then an alternative non-foveating system for making eye movements is being employed.
This section will address the part of hypothesis 2 which reads "Foveating saccades will be suppressed and eye movements will be made directly to the PRL rather than to the scotoma."

8.4.1 Effect of age and macular disease on saccadic latency and velocity
Saccadic latency and velocity for patients and age-matched control subjects at the baseline assessment is shown in table 8.2.

Analysis of variance reveals a significant increase in saccadic latency with age (p<0.05), regardless of the presence of disease. However, the presence of disease does not increase saccadic latency (p=0.20). There is no interaction between age and disease when entering these variables as an interaction term in the ANOVA (p=0.76).

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean(sd) saccadic latency (msec)</th>
<th>Mean(sd) peak saccadic velocity (°/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMD</td>
<td>230 (79)</td>
<td>501 (112)</td>
</tr>
<tr>
<td>Older controls</td>
<td>188 (58)</td>
<td>437 (113)</td>
</tr>
<tr>
<td>JMD</td>
<td>186 (66)</td>
<td>379 (73)</td>
</tr>
<tr>
<td>Younger controls</td>
<td>137 (25)</td>
<td>473 (105)</td>
</tr>
</tbody>
</table>

Table 8.2. The effect of macular disease and age on saccadic latency and velocity.

Neither age nor macular disease has any effect on the peak saccadic velocity at the baseline assessment (ANOVA, F(df=3,32)=1.92, p=0.15; table 8.2).

8.4.2 Saccadic latency, saccadic velocity and reading speed
At the baseline assessment, there was no linear relationship between reading speed and saccadic latency for AMD patients (r = -0.32, p=0.20) or JMD patients (r = -0.42, p=0.58). There is no relationship between saccadic velocity and reading speed for patients at the baseline assessment (r = -0.10, p=0.64). These data are shown in figure 8.8.
Figure 8.8. Upper panel: Saccadic latency and reading speed for AMD patients (filled symbols) and JMD patients (open symbols) at baseline. n=24 (excludes AP). Lower panel: Saccadic velocity and reading speed for all patients at baseline. n=24 (excludes AP).
8.4.3 Changes in saccadic latency and velocity with time

Chapter 5 of this thesis has shown that saccadic latency and velocity remain constant over the course of the study in control subjects (table 5.4). Similarly, no systematic change occurs over time in patients' saccadic latency or velocity (repeated measures ANOVAs: saccadic latency, 0-6 months, p=0.31; 0-12 months, p=0.32. Saccadic velocity, 0-12 months, p=0.38). These data are shown graphically in figure 8.9.

It can be seen from the lower panel of figure 8.9 that there appears to be a drop in the mean saccadic velocity value between one and three months. However, this finding does not reach significance (repeated measures ANOVA, 0-3 months p=0.07).

Although there is no systematic change in saccadic latency or accuracy, in some subjects latency or velocity changed by a large amount in this study. Figure 8.10 shows the individual changes in latency and velocity between the baseline and exit point of the study.

The hypothesis states that as patients suppress their foveating saccade mechanism, saccadic latency will increase and the peak velocity of saccades will fall. Patients who behaved as hypothesized are shown in red on both panels of figure 8.10.
Figure 8.9. Upper panel: Change in saccadic latency with time, by group. Error bars show one standard deviation. Open symbols show JMD patients, filled symbols show AMD patients. Lower panel: Changes in saccadic velocity with time. Error bars show one standard deviation.
Figure 8.10. **Upper panel:** Change in saccadic latency between baseline and exit for each patient. Red lines show patients where latency increased by ≥10%. **Lower panel:** Change in saccadic velocity between baseline and exit for each patient. Red lines show patients where velocity decreased by ≥10%. n=20 for both panels due to computational limitations.
8.4.4 Discussion

8.4.4.1 Saccadic latency and velocity at baseline

At the baseline assessment, there is a significant increase in saccadic latency with age but the presence of macular disease does not significantly affect saccadic latency. Comparison of the baseline latencies for young and old subjects indicates that the increase in saccadic latency with age is equivalent to 1.6 msec/year. This is consistent with the results of previous studies (Abel et al., 1983; Carter et al., 1983; Pitt & Rawles, 1988). As patients aged by one year over the course of this study, their saccadic latency may have risen by 1 or 2 msec between the baseline and 12 month follow up visits. This effect is too small to be observed in the data presented in this chapter.

Although there are no between-groups differences in saccadic latency, some patients demonstrate very long latencies (figure 8.10, upper panel). Six patients’ saccadic latency are longer than the upper 95th centile for age-matched control subjects (249 msec for the older controls, 177 msec for the younger subjects). These patients are RG, BP, MA, KD, AP and MF.

Saccadic latencies found for patients throughout this study are shorter than those in the Whittaker, Cummings and Swieson study (1991). One reason for this difference is that the amplitude of the saccades was different; in Whittaker’s study, the target was presented at a random location of between 1 and 35° decentration, whereas in the present study target decentration was only 18°. As saccadic latency increases with increased saccadic amplitude (Carpenter, 1988), latency will be higher for the task described in the paper by Whittaker et al. Patient instruction was also different between the two studies; participants in Whittaker’s study were asked to make a judgement about the target which they were observing whereas the subjects in this study were merely asked to “look at the target”.

The method of random target presentation in any position within 35° used by Whittaker would sometimes project the target within the scotoma. Saccades to unseen targets take far longer to execute than those to visible targets (Hallett, 1986; Carpenter, 1988). This would also contribute to the longer mean latencies found in
Whittaker's patients.
Saccadic velocity is equal in patients and age-matched control subjects at the baseline visit. The values for saccadic velocity for patients found in this chapter are similar not only to those for the age-matched control subjects but also to those found for normal observers in different studies (see Carpenter, 1988, for a review). This implies that the difference in results is due to the patients in this study behaving differently to those in Whittaker’s 1991 and White’s 1990 papers, rather than the control subjects being particularly poor.

8.4.4.2 Foveating or non-foveating saccades?
The motivation for examining saccadic latency and velocity at each visit in this study was to determine whether patients are using a foveating or non-foveating saccade mechanism. Whittaker suggests that with time, patients suppress their foveating saccades and that slower, non-foveating saccades are adopted.

Although there is no systematic change in saccadic latency or velocity in this study, as figure 8.10 has shown some patients experienced large changes in these variables.

Figure 8.11 below shows the correlation between changes in saccadic latency and velocity between the baseline and final assessment for each patient in this study. If patients are adopting a non-foveating saccade mechanism their saccadic latency will increase and their velocity will fall; that is, they will be clustered into the lower right hand quadrant of figure 8.11.
Figure 8.11. Change in saccadic latency and velocity between baseline and exit. n=25.

It can be seen that six patients fall into this area. They are CT, HP, IP, JY, PF and RS. A further three patients experience an increase in saccadic latency without a corresponding decrease in saccadic velocity (patients AS, EC and SG).

The velocity of saccades in patients with macular disease has only ever been measured by Whittaker et al (1991). Closer examination of Figure 5 in the paper by Whittaker reveals that although there is a trend for patients' saccades to be slower than control subjects', there is a very considerable overlap between the two groups. Further, no statistically significant differences in saccadic velocity are reported by Whittaker. It is therefore suggested that all nine of the patients whose saccadic latency increased in the present study can be said to have developed non-foveating saccades.

These nine patients have been added to the six patients described in section 8.4.4.1, and are classified as those who are making non-foveating saccades. There is no difference between these fifteen patients and the remaining ten in terms of disease type ($\chi^2$ test, p=1.00), visual acuity (p=0.93) or scotoma size (p=0.52). There was no association with pseudofoveation ($\chi^2$ test, p=0.41), and changes in saccadic latency were not associated with changes in saccade efficiency ($r^2=0.09$).
All but one of the patients in the study of White and Bedell experienced a saccadic latency outside normal limits (White & Bedell, 1990). It is unclear whether the patients in the present study will exhibit a slower saccadic latency with more time. The one patient in Whittaker's study who did not display an increase in saccadic latency had a 12-month history of AMD. This implies that the adaptation may take longer than the follow-up period of this study in some patients.

The assumption that these patients are making non-foveating saccades is based on data collected from the infra-red eyetracker, so the retina was not being viewed during this experiment. The experiment was designed in this manner to allow greater accuracy in the measurement of saccadic latency and accuracy; the temporal resolution of the eye-tracker is 5 times more precise than the SLO.

Simultaneous high-frequency eyetracking and retinal observation would be an ideal mechanism for determining the presence of foveating and non-foveating saccades. Methods for this procedure are discussed in chapter 15.

8.5 Summary of chapter 8

Section 8.3 of this chapter has shown that patients display a lower saccadic efficiency when compared to subjects without macular disease. This lower efficiency appears to be related to the impairment in reading speed experienced by patients with central scotomas. In eight patients, saccade efficiency reached normal values.

Most patients (76%) still make foveating saccades at their baseline assessment. Over time, a further nine patients modify this mechanism and by the exit point of the study, 60% of the patients repeatably make saccades which display the latency characteristics of non-foveating saccades.
There is no association between these two adaptive strategies, they appear to be independent. The benefit of each of these adaptations in terms of reading speed will be assessed in chapters 10 and 11 of this thesis.

This chapter has shown that the first part of hypothesis 2 is true for some patients. An updated version could read: "In certain patients, the number of saccades used to locate a target will reduce over time, whilst in some patients foveating saccades will be suppressed and eye movements will be made directly to the PRL rather than to the scotoma."
Chapter 9: Eye movements made whilst reading

The previous chapter has shown that more saccades are made to view a target in the presence of a central scotoma. This chapter will investigate eye movements made by patients and control subjects when reading. Reading speed is the primary outcome measure of this thesis and a reduction in reading ability is the most frequent complaint of patients with macular disease (section 1.2.3).

Bullimore and Bailey (1995) used an infrared eyetracker to examine horizontal saccade patterns made whilst reading in 13 patients with AMD and six age-matched control subjects. They found that the number of forward saccades was greatly increased in patients, from one saccade per six letters of text in control subjects to one saccade per three letters in certain patients. Bullimore attributed this difference to a reduction in the width of the perceptual span; as fewer letters are identified per fixation, more saccades are required. Bullimore and Bailey also found a large increase in the number of regressive saccades in patients, although they conceded that these right-to-left saccades may actually be eye movements made to switch between multiple PRLs rather than true regressions.

The study of eye movements by McMahon and colleagues has already been described in chapter 8. Although eye movements were not recorded during reading in McMahon's study, they were measured whilst fixating five spaced letters in sequence, which is a similar task to reading. McMahon found that the number of saccades used for this task was linearly related to reading speed, with a correlation coefficient of -0.89 (McMahon et al., 1993).

Bowers and colleagues examined both the saccadic frequency rate in the manner described by McMahon and the number of saccades made when reading. They found that the number of saccades used whilst reading was very strongly related to reading speed \( (r = -0.97) \), whereas the number of saccadic properties to observe a target were less well correlated \( (r = -0.57) \). They found a linear relationship between
these two variables \( (r = 0.55) \) (Bowers et al., 2001).

The relationship between fixation duration and reading speed in macular disease is less well established. In subjects with simulated visual impairment, the length of each fixation duration increases from about 300 to about 450 msec as the level of impairment is increased and reading speed slows (Bowers & Reid, 1997). Bowers found that fixation duration is linearly related to reading speed in these observers \( (r=-0.86) \). Further, Trauzettel-Klosinski and colleagues found an increase in fixation duration in patients with Stargardt disease when compared to control subjects (Trauzettel-Klosinski et al., 1994).

However, Bullimore and Bailey did not find a significant increase in fixation duration in patients with macular scotomas; patients and control subjects had a typical fixation length of around 300 msec.

This chapter will investigate the number of forward and regressive saccades used to read a sentence, the number of saccades needed to find the start of each line of text and the fixation duration of the patients examined in this study. The importance of these parameters in determining reading speed will be investigated. This chapter will also examine the change in these variables with time, to address the second part of hypothesis 2: "Eye movement control will become more efficient when reading; with time, fewer saccades will be required to read a sentence, and the number of regressive saccades made during a reading task will also fall."

A general discussion of the results can be found in section 9.4 below. Full data can be found in appendix 1 section A1.9.

9.1 Specific methods

Eye movements were recorded using the Eyelink gazetracker whilst patients read MN-Read style sentences presented at 3x acuity, as described in sections 2.4.1 and 2.5.2.4. The sentences were 55 characters long and were divided over two lines. Retrospective analysis of the data recorded by the eyetracker identified the number of forward saccades, the number of regressive saccades, the number of saccades to
find the start of each line of text and the time taken to read the sentence. Fixation
duration was calculated using the following formula:

\[
\text{Fixation duration} = \frac{\text{Time taken to read the sentence}}{\text{(Total number of saccades +1)}}
\]

This formula uses one more than the number of saccades as the denominator to
account for the fixation made after the final saccade of the trial. Several methods
exist for calculating fixation duration; this formula has been used by Bullimore and
Bailey (1995). This formula is liberal in that any time when the eye is not making a
saccade will be classified as a fixation. Fixation duration will be longer when
calculated by this formula than when using the method of, for example, Rayner
(1978). Each parameter was recorded for each sentence, and mean values for all ten
sentences were used for the analyses in this chapter.

9.2 The number of saccades used whilst reading

9.2.1 The effect of macular disease on eye movements when reading
At the baseline assessment, the number of forward saccades used to read a sentence
was doubled in patients with macular disease, from a mean value of 8.0 in control
subjects to 16.0 saccades in patients \((p<0.001)\). The number of regressive saccades
also increased (from 0.8 to 5.0 saccades; \(p<0.05\)), as did the number of saccades
needed to find the start of a line (1.2 to 3.1 saccades; \(p<0.001\)). There is a
considerable variability in these results between patients, as can be seen in figure
9.1.

Age has no effect on any of these variables in patients or in control subjects
(Student's t-test comparing older to younger participants: patients: number of
forward saccades \(p=0.38\); number of regressive saccades \(p=0.47\); number of
saccades to the start of a line \(p=0.30\). Control subjects: number of forward saccades
\(p=0.37\); number of regressive saccades \(p=0.09\); number of saccades to the start of a
line \(p=0.50\).

Further, the type of macular disease has no effect on these three variables (ANOVA;
number of forward saccades \(F_{(df 2, 24)}=0.73, p=0.49\); number of regressive saccades
\(F_{(df 2, 24)}=2.82, p=0.08\); number of saccades to the start of a line \(F_{(df 2, 24)}=1.76,\)
Figure 9.1. Number of forward saccades (Forward), number of regressive saccades (Regressive) and the number of saccades to the start of a line (To start) for patients and control subjects at the baseline assessment. Error bars show one standard deviation.

Figure 9.2 shows a scatterplot matrix for these three variables. It can be seen that there is a relationship between the number of forward saccades, the number of regressive saccades and the number of saccades used to find the start of a line. Spearman's test confirms there is a strong rank correlation between these variables (table 9.1).

| Variable 1     | Variable 2     | Correlation coefficient | \( p > |\rho| \) |
|----------------|----------------|-------------------------|------------------|
| N regressive   | N forward      | 0.72                    | <0.0001          |
| N to start     | N forward      | 0.53                    | <0.01            |
| N to start     | N regressive   | 0.63                    | <0.001           |

Table 9.1. Spearman's rho coefficients between number of regressive saccades (N regressive), number of forward saccades (N forward) and number of saccades to the start of each line (N to start) for all patients at the baseline assessment.
Forward saccades

Regressive saccades

Saccades to start

9.2.2 The relationship between eye movements when reading and when observing a target

There is no relationship between the number of forward saccades used to read a sentence and either saccadic latency or velocity when observing a target (linear regression: saccadic latency, \( r = -0.08, p=0.72 \); saccadic velocity, \( r = 0.00, p=0.91 \)). Similarly, no relationship exists for regressive saccades (latency, \( r = 0.07, p=0.75 \); velocity, \( r = 0.15, p=0.49 \)) or for the number of saccades to the start of a line (latency, \( r = 0.26, p=0.29 \); velocity, \( r = 0.26, p=0.31 \)).

There is a linear relationship between saccadic efficiency (as described in section 8.3) and the number of forward saccades used to read a sentence (linear regression, \( r \))
= 0.59, p<0.01; figure 9.3). This relationship is not as pronounced for either the number of regressive saccades (r = 0.17, p=0.39) or for the number of saccades required to find the start of a line (r = 0.37, p=0.07).

**Figure 9.3.** The relationship between the number of forward saccades when reading a sentence and saccadic accuracy, for all patients at the baseline assessment. Line shows linear regression. n=24.

### 9.2.3 The relationship between eye movements when reading and reading speed

There is a strong linear relationship between the number of forward saccades used to read a sentence and patients' reading speed at the baseline assessment (r = -0.71, figure 9.4). Similar relationships exists for the number of regressive saccades (r = -0.72) and for the number of saccades used to find the start of a line (r = -0.80).
9.2.4 Change in the number of saccades used for reading with time

In control subjects, the number of saccades used to read a sentence remained stable over one year at 7.9 saccades (see table 5.4). In patients, no systematic change was found in the number of forward saccades, the number of regressive saccades or the number of saccades used to find the start of each line (repeated measures ANOVA, table 9.2, figure 9.5). It can be seen from figure 9.5 that variance in the number of forward saccades falls after the 3 month visit, although there is no systematic change in the standard deviation of the number of saccades ($r = -0.4$; $p=0.43$).

Although there was no systematic change, in certain individuals the number of saccades used for reading does change. There is a negative linear relationship between a change in the number of forward saccades used to read a sentence and a change in reading speed ($r = -0.41$). This effect is more pronounced for the number of regressive saccades ($r = -0.46$) and for the number of saccades used to find the start of the line ($r=-0.53$).
These changes are not correlated with changes in saccade efficiency (linear regression; forward saccades $r = 0.00$, $p=0.84$; regressive saccades $r = 0.10$, $p=0.73$; to the start of a line $r = 0.39$, $p=0.09$) or saccadic latency (linear regression; forward saccades $r = -0.20$, $p=0.38$; regressive saccades $r = -0.10$, $p=0.67$; to the start of a line $r = -0.28$, $p=0.23$).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Repeated measures ANOVA, p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 to 6 months</td>
</tr>
<tr>
<td>Number of saccades</td>
<td>0.72</td>
</tr>
<tr>
<td>Number of regressive saccades</td>
<td>0.26</td>
</tr>
<tr>
<td>Number of saccades to start of line</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Table 9.2. Repeated measures ANOVA for reading parameters between 0 and 6 months and 0 and 12 months, for all patients.

Figure 9.5. Changes in the number of forward saccades to read a sentence (Forward), the number of regressive saccades to read a sentence (Regressive) and the number of saccades to the start of each line (To start) over time, for all patients. Error bars show one standard deviation.
9.3 Fixation duration

9.3.1 The effect of age and macular disease on fixation duration at baseline
Mean fixation duration for patients and control subjects can be seen in figure 9.6 below. There is no difference in fixation duration between these four groups (ANOVA, $F(df=3, 30)=1.27$, $p=0.30$).

![Figure 9.6. Fixation duration at the baseline assessment, for all patients and control subjects. Error bars show one standard deviation.](image)

9.3.2 The relationship between fixation duration and reading speed
Fixation duration is not related to the number of saccades used by patients to read a sentence (linear regression, $r = 0.10$, $p=0.61$), to the number of regressive saccades ($r = 0.20$, $p=0.39$), or to the number of saccades used to find the start of each line ($r = 0.40$, $p=0.08$). There is, however, a relationship between fixation duration and reading speed in patients; patients with longer fixation duration read more slowly than those with shorter fixations ($r = -0.62$, $p<0.01$; figure 9.7). A similar trend
exists in control subjects ($r = -0.66$, $p=0.05$). Figure 9.7 shows both of these relationships. The gradient of the line of best fit is -0.18 for patients and -0.27 for control subjects.

**Figure 9.7.** The relationship between fixation duration and reading speed for patients (filled symbols, heavy line) and control subjects (open symbols, light line). $n=33$.

Under the paradigm used for determining fixation duration in this experiment, each fixation comprises the time to identify the word or syllable being fixated and the latency time of the following saccade. To ensure that variance in fixation duration was not accounted for by the individual differences in saccadic latency, linear regression was performed to compare saccadic latency length to fixation duration. Saccadic latency accounts for 24% of the variance in fixation duration in patients, so the length of each fixation is due in part to the latency of each saccade.

### 9.3.3 Changes in fixation duration with time

Chapter 5 of this thesis has shown that fixation duration remains unchanged in control subjects throughout this study (table 5.4). Figure 9.8 shows the change in fixation duration with time for patients. Repeated measures analysis of variance does not indicate any systematic difference in reading speed (0-6 months, $p=0.87$; 0-
12 months, p=0.90).

![Figure 9.8. Change in fixation duration with time for patients. Error bars show one standard deviation.](image)

### 9.4 Discussion

#### 9.4.1 The number of saccades used when reading

There is an association between the number of forward saccades used to read a sentence, the number of regressive saccades used when reading a sentence and the number of saccades required to find the start of each line of text. These variables are all significantly increased in the presence of macular disease.

The number of forward saccades accounts for 51% of the variance in reading speed in this study; similar to that described by McMahon and colleagues ($r^2=0.80$, $n=14$; (McMahon et al., 1993)). The patients in McMahon’s study demonstrated a reduction in the number of saccades used and an increase in reading speed with training. Although there were no systematic changes in the saccadic properties when reading for the patients in the present study, these subjects did not receive any active intervention or training. The potential benefit of training has been alluded to in the previous chapter and will be described fully in chapter 13.

Bullimore and Bailey’s 1995 paper described a strong linear correlation between reading speed and the number of letters read per forward saccade (an equivalent measure to the number of forward saccades in this analysis). Bullimore and Bailey
suggested three hypotheses for this increase in the number of saccades; first that the perceptual span is reduced so fewer letters are attended per fixation; second, that patients’ ability to direct their eyes is impaired and finally that the ability to integrate information across saccades is impaired.

The visual span hypothesis discussed by Bullimore and Bailey would predict that the number of saccades used to read a sentence would increase. However, it would not predict an increase in the number of saccades needed to find a small point target, as the perceptual span requirement for this task is far smaller. This chapter has shown that there is a strong relationship between the number of saccades used to read a sentence and the number of saccades used to view a point target. These data suggest that the difficulty in reading is not solely attributable to the shrinking visual span hypothesis.

The data presented in this chapter lend most support to the second of Bullimore’s hypotheses, that difficulty in guiding saccades is the primary factor which increases the number of eye movements when reading with a central scotoma. The ability to integrate information across saccades has not been directly assessed by this experiment, so Bullimore’s third hypothesis can not be tested.

9.4.2 Fixation duration
This study has not found fixation duration to be significantly increased in patients with macular disease when compared to control subjects. This finding is similar to that of Bullimore and Bailey (1995) who found fixation rate (the reciprocal of fixation duration) to be similar in patients with AMD and control subjects.

As figure 9.7 shows, fixation duration influences reading speed by a similar amount in both control subjects and patients. Individual differences in fixation duration are well known to influence reading speed (Rayner, 1978; Rayner, 1998). It is tempting to speculate that the individual differences in fixation duration between these patients are independent of the presence in macular disease. As the fixation duration of these patients before the onset of the scotoma is not known, this hypothesis remains conjecture. One method for assessing the relationship between fixation duration and reading speed would be to remove the need for saccades, either by
presenting text with the RSVP technique or by scrolling text whilst patients’ eyes remained steady. This would have been an ideal control condition for this section of the study; unfortunately this was not considered at the outset of this project.

9.4.3 The relative importance of each variable
Variance in reading speed is related to all of the factors discussed in this chapter: the number of forward saccades \((r^2 = 0.51)\), the number of regressive saccades \((r^2 = 0.52)\), the number of saccades to find the start of a line \((r^2 = 0.64)\) and fixation duration \((r^2 = 0.39)\). To determine the relative importance of these four factors, multivariate regression was performed using the techniques described in chapter 10. The model was constructed using forwards and backwards regression, and is shown in table 9.3. The model indicates that the number of forward saccades, the number of regressive saccades and fixation duration combine to account for 87% of the variance in reading speed.

<table>
<thead>
<tr>
<th>Step</th>
<th>Variable</th>
<th>Cumulative (r^2) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Number of forward saccades</td>
<td>0.51</td>
</tr>
<tr>
<td>2</td>
<td>Number of regressive saccades</td>
<td>0.59</td>
</tr>
<tr>
<td>3</td>
<td>Fixation duration</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Table 9.3. Result of statistical regression

Although reading speed can be predicted to a high degree of accuracy using this technique, this model suffers from a cause and effect problem; it is not clear whether the increase in the number of saccades and fixation duration are a cause of slow reading or a consequence of it. To overcome this paradox in this study, models have been constructed to determine reading speed using variables measured for other tasks. These findings are presented in the next chapter.

9.5 Conclusion

The number of forward saccades, number of regressive saccades and number of saccades to find the start of a line are covariant in the patients seen in this study. These variables are, in turn, linearly related to reading speed of patients with macular disease. There is a strong relationship between the number of saccades used
to read a sentence and the number of saccades used to view a target. This chapter supports the hypothesis that impairment of eye movement control is a key cause of the reduction in reading speed of patients with macular disease.

No systematic difference is found in any of these parameters over time. This chapter has failed to support that part of hypothesis 2 which states that “eye movement control will become more efficient when reading; with time, fewer saccades will be used to read a sentence, and the number of regressive saccades made during a reading task will also fall.”
Chapter 10: Cross-sectional analysis: Factors which predict reading speed

Chapters 5 to 8 of this thesis have shown that, at the baseline assessment, the presence of macular disease impairs performance on clinical tests, reduces the stability of fixation and increases saccadic inefficiency. This chapter uses multivariate statistical techniques to investigate the contribution of these factors to the reduction in reading speed experienced by patients with central scotomas.

Previous attempts to predict reading speed in patients with AMD have had varying degrees of success (table 10.1). (Cummings, Whittaker, Watson & Budd, 1985; Legge, Ross, Isenberg & LaMay, 1992; McMahon, Hansen, Stelmack, Oliver & Viana, 1993; Bullimore & Bailey, 1995; Fine & Rubin, 1999; Fletcher, Schuchard & Watson, 1999; Bowers, Lovie-Kitchin & Woods, 2001; Ergun, Maar, Radner, Barbazetto, Schmidt-Erfurth & Stur, 2003).

<table>
<thead>
<tr>
<th>Group</th>
<th>Predictors</th>
<th>Patients (n)</th>
<th>Variance in reading speed accounted for ($r^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cummings et al (1985)</td>
<td>Scotoma size</td>
<td>18*</td>
<td>0.45</td>
</tr>
<tr>
<td>Legge et al (1992)</td>
<td>Visual acuity Age</td>
<td>45</td>
<td>0.32</td>
</tr>
<tr>
<td>McMahon et al (1993)</td>
<td>Saccadic efficiency</td>
<td>12</td>
<td>0.79</td>
</tr>
<tr>
<td>Bullimore &amp; Bailey (1995)</td>
<td>Letters/forward saccade</td>
<td>13</td>
<td>0.92</td>
</tr>
<tr>
<td>Sunness et al (1997)</td>
<td>Scotoma size Visual acuity</td>
<td>44*</td>
<td>0.43</td>
</tr>
<tr>
<td>Fine &amp; Rubin (1999)</td>
<td>Scotoma size** Visual span**</td>
<td>8</td>
<td>0.42</td>
</tr>
<tr>
<td>Fletcher et al (1999)</td>
<td>Visual acuity “Scotoma characteristics”</td>
<td>99</td>
<td>0.33</td>
</tr>
<tr>
<td>Bowers et al (2001)</td>
<td>Saccadic efficiency</td>
<td>21</td>
<td>0.34</td>
</tr>
<tr>
<td>Ergun et al (2003)</td>
<td>Scotoma size</td>
<td>22</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Table 10.1. Previous models of reading speed in patients with MD. *: estimated, number of eyes only reported. **: simulated impairments.
Chapter 10: Cross-sectional example

The example in Chapter 10 illustrates a cross-sectional study design. In a cross-sectional study, data is collected at a single point in time. This type of study is useful for examining the distribution of a disease or health condition in a population at a specific time. The data collected can be used for descriptive purposes, to understand the prevalence of the disease, or to identify risk factors associated with the disease.

The table below provides an overview of the prevalence of a certain condition across different age groups and genders. The data is presented as a percentage of the population affected.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Gender</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-30</td>
<td>Male</td>
<td>12%</td>
</tr>
<tr>
<td>31-40</td>
<td>Female</td>
<td>15%</td>
</tr>
<tr>
<td>41-50</td>
<td>Male</td>
<td>20%</td>
</tr>
<tr>
<td>51-60</td>
<td>Female</td>
<td>25%</td>
</tr>
<tr>
<td>61-70</td>
<td>Male</td>
<td>18%</td>
</tr>
<tr>
<td>71-80</td>
<td>Female</td>
<td>20%</td>
</tr>
</tbody>
</table>

The prevalence data is based on a sample of 1,000 individuals from a diverse population. The study was conducted over a period of one year, and the results are presented as a percentage of the population at risk.
This chapter will use the variables which have been discussed measured in chapters 5-8 to predict reading speed. The results presented in chapter 9 have not been used in this chapter due to the cause and effect problem discussed in section 9.4.3.

Section 10.2 of this chapter will examine reading speed at the baseline assessment and section 10.3 will predict reading speed at the exit point of the study.

The results presented in this chapter are the first to examine the factors which limit reading speed in patients with newly developed macular disease. This section will address hypothesis 3, that "the measurement of clinical, fixation and eye movement variables in this study will improve the prediction of reading speed in patients with central scotomas."

10.1 Specific method

Multivariate statistical regression was performed on the variables measured in chapters 5 to 8 (table 10.2) with reading speed being the outcome measure. Systat (v.10.2.05, Systat software, Richmond, CA, USA) was used for all of the analyses in this section. The Systat “regress” function was used for the multivariate analysis. Entrance and exit criteria were set to 0.15 and the model was constructed both forwards and backwards. A constant was added into the model so that the model was not constrained to pass through the origin.

After each model was constructed, the distribution of residual values was plotted. Examination of the residual plot can indicate whether there is any failure of normality, nonlinearity or heteroscedasticity amongst the data (Tabachnick & Fidell 2001, p. 120). Finally, as the sample size is relatively small when compared to the number of variables used, the Systat “boot” command was used to bootstrap the data. Bootstrapping is a process by which samples are drawn at random from the data set and the validity of the model is assessed (Tabachnick & Fidell, 2001).
### Table 10.2. Variables entered into the stepwise model.

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Dependent variable (Outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distance visual acuity (logMAR)</td>
<td>Reading speed (sentences presented at 3x threshold acuity, words/minute)</td>
</tr>
<tr>
<td>Contrast sensitivity (log units)</td>
<td></td>
</tr>
<tr>
<td>Scotoma size (disc areas)</td>
<td></td>
</tr>
<tr>
<td>Fixation stability (logBCEA)</td>
<td></td>
</tr>
<tr>
<td>Presence of pseudofoveation (yes/no; nominal variable)</td>
<td></td>
</tr>
<tr>
<td>Using a repeatable number of PRLs (yes/no; nominal)</td>
<td></td>
</tr>
<tr>
<td>Saccadic efficiency (number of saccades)</td>
<td></td>
</tr>
<tr>
<td>Saccadic latency (msec)</td>
<td></td>
</tr>
<tr>
<td>Saccadic velocity (°/sec)</td>
<td></td>
</tr>
</tbody>
</table>

#### 10.2 Baseline reading speed

##### 10.2.1 Model constructed

Statistical regression indicated the presence of the same model when run forwards and when run backwards. A combination of three variables can predict reading speed to an $r^2$ value of 0.68. These factors were saccadic accuracy, fixation stability and scotoma size (table 10.3).

<table>
<thead>
<tr>
<th>Step</th>
<th>Variable</th>
<th>Cumulative $r^2$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Saccadic efficiency</td>
<td>0.39</td>
</tr>
<tr>
<td>2</td>
<td>Fixation stability</td>
<td>0.61</td>
</tr>
<tr>
<td>3</td>
<td>Scotoma size</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Table 10.3. Result of statistical regression.

The model predicted from this analysis was:

$$RS = 292 - 33.7SE - 13.8FS - 7SS$$

(Eq. 10.1)

Where RS=reading speed, FS= fixation stability, SE= saccadic efficiency and SS= scotoma size. Predicted reading speed is compared to actual reading speed in figure 10.1.
Figure 10.1. Scatterplot of predicted reading speed (using equation 10.1) against actual reading speed for all patients at the baseline assessment.

10.2.2 Validity of the model
Multivariate analysis can be weighted by outlying data. For this reason, it is important to assess the distribution of residual data for any analysis. This distribution is shown in figure 10.2. There is no failure of normality, nonlinearity or heteroscedasticity amongst these data (Tabachnick 2001, p.120).
Statistical regression can also be biased by collinearity between the predictor values. Pairwise analysis of the variables indicates that there is a linear relationship between saccadic efficiency and scotoma size in these patients at the baseline assessment ($r = -0.40$, $p=0.05$). However, the fact that the same model is constructed by forward and backward regression confirms that both of these variables independently contribute to the prediction of reading speed (see Tabachnick 2001, p.142).

Bootstrapping the data, using 1000 repetitions, revealed a Durbin-Watson D statistic of 2.34, giving a first order autocorrelation of -0.27. This indicates that the model does not contain nonindependent errors (personal communication, Dr Edmond Ng, 2004).

10.3 Exit reading speed

Figure 10.3 below shows the difference between baseline reading speed and reading speed at the exit point of the study for the patients seen in this study. There is a
weak relationship between baseline and exit reading speed (repeated measures ANOVA, p=0.13).

![Figure 10.3. Difference between exit and baseline reading speed for all patients.](image)

Using the model defined in equation 10.1, 33% of the variance in reading speed is accounted for. As reading speed at the exit point may be predicted by factors other than those which limit baseline reading speed, the model construction performed in section 10.2 above was repeated, using the same independent variables, to predict exit reading speed.

### 10.3.1 Model constructed

The model constructed by this analysis was similar to that in equation 10.1. Again, the same model was created by forward and backward multiple regression. This model can predict reading speed with an $r^2$ value of 0.59. It contains three independent variables: fixation stability, saccade efficiency and contrast sensitivity (table 10.4).
The model predicted from this analysis was:
\[ RS = 299 - 14FS - 16.6SE + 65CS \]  
(Eq. 10.2)

Where RS=reading speed, FS= fixation stability, SE= saccadic efficiency and CS=contrast sensitivity.

10.3.2 Validity of the model

Figure 10.4 shows the plot of residuals against predicted values for this model.

Again, no failure of normality, nonlinearity or heteroscedasticity amongst these data is seen.

No colinearity exists between the variables in the model given in equation 10.2. Bootstrapping with 1000 repetitions gives a Durbin-Watson D statistic of 1.28 and first-order correlation of 0.23. This confirms that there are no nonindependent errors in the model.
10.4 Discussion

The model presented here shows that nearly 70% of the variance in reading speed at baseline can be accounted for by three variables; saccadic accuracy, fixation stability and scotoma size.

By the exit point of the study, the relative importance of these variables has changed; fixation stability replaces saccadic accuracy and scotoma size has been replaced by contrast sensitivity in the model. 60% of the variance in exit reading speed can be predicted by these variables.

One significant factor which has not been measured in this study is patients' psychological adaptation to their vision loss. Patients are known to follow a grieving process immediately after losing central vision (section 1.2.3). As patients move to the stage of acceptance to their visual loss, it is likely that their motivation, and consequently their reading speed may improve. This important limitation is discussed further in chapter 13.

The predictor values illustrated in table 10.4 are similar to those suggested by Schuchard, Naseer and de Castro in their "PRL scoring system" to predict rehabilitation in macular disease. Schuchard’s system includes two of the measures described here: fixation stability and "saccadic movement score" which determines how many saccades are used to fixate a target with the PRL (Schuchard, Naseer & de Castro, 1999). However, Schuchard has never applied this scoring system to examine reading speed.

In the present study, factors measured during the reading process were deliberately not entered into the model. This was to avoid using reading speed to predict reading speed; for example, the increase in the number of saccades used to read a sentence may be a predictor for slower reading but it may also be a consequence of slower reading.

Bullimore and Bailey (1995) did not have these reservations when constructing their model which accounts for the higher correlation coefficients found in their analysis.
Bowers and colleagues performed two separate analyses of reading speed: one using saccadic variables from a reading task \( (r^2 = 0.94) \) and one using the parameters of saccades made during a different task \( (r^2 = 0.34) \).

In a similar fashion, if the number of forward saccades whilst reading is used to predict reading speed in the present study, 80% of the variance in exit reading speed is accounted for.

McMahon found a stronger correlation between saccadic efficiency and reading speed than was found in the present study (McMahon: \( r = -0.89 \); this study: \( r = -0.62 \)). However, the cohort of subjects described in table 10.1 above are those who have received saccadic training. This may account for a stronger correlation than that found in this study.

Scotoma size limits baseline reading speed but over time, contrast sensitivity replaces Scotoma size in the model. Contrast sensitivity and Scotoma size are not closely related \( (r = 0.14) \). This implies that although patients with larger scotomas read more slowly immediately after Scotoma development, other adaptive strategies become more important in determining how well patients read.

These models have predicted reading speed at two points in time; at presentation and at the exit point of the study. Figure 10.3 shows that reading speed changes over time. The difference between the two models given above has shown that the factors which limit reading speed, and their relative importance, also change with time.

Chapter 11 will examine the change in reading speed in patients in more detail and will determine what factors account for this change in reading speed.

10.4.1 Conclusion

This chapter has performed the first analysis of which factors limit patients' reading speed when they first develop macular disease. At presentation, saccadic efficiency, fixation stability and Scotoma size are the most important factors in determining reading speed, together accounting for 70% of the variance in patients' reading speed.
speed.

Over time, patients' reading speed changes. At the exit point of the study, fixation stability, saccadic efficiency and contrast sensitivity are the most powerful predictors of reading speed, together accounting for 60% of the variance in reading speed. This model is similar to one previously suggested by Schuchard and colleagues.

This chapter has confirmed hypothesis 3, that “the measurement of clinical, fixation and eye movement variables in this study will improve the prediction of reading speed in patients with central scotomas.”
Chapter 11: Longitudinal analysis: Factors which predict change in reading speed

Chapter 10 has shown that reading speed changes in patients between their entrance and exit visits. This chapter will provide a longitudinal analysis of reading speed in each patient. It will analyse changes in the variables described in chapters 5 to 8, and will determine which of these changes lead patients to experience an improvement, or a deterioration, in reading speed.

Figure 11.1 shows the changes in reading speed over time for the AMD patients. These figures have been normalised, with reading speed at each visit being shown in relation to baseline reading speed. Patients whose reading speed ultimately increases by more than 27% are shown in red, those who exhibit a similar decrease are shown in blue and those with no change are shown in black. Section 5.3 has described the basis for using 27% as the threshold for determining a clinically significant change.

Table 11.1 below shows in which patients reading speed improves, stays the same or deteriorates over the course of the study.

<table>
<thead>
<tr>
<th>Reading speed improves by ≥27%</th>
<th>Reading speed stays within 27%</th>
<th>Reading speed deteriorates by ≥27%</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS</td>
<td>AP</td>
<td>JM</td>
</tr>
<tr>
<td>FG</td>
<td>BP</td>
<td>JW</td>
</tr>
<tr>
<td>PF</td>
<td>CT</td>
<td>KD</td>
</tr>
<tr>
<td>RH</td>
<td>HP</td>
<td>MA</td>
</tr>
<tr>
<td></td>
<td>JA</td>
<td>MF</td>
</tr>
<tr>
<td></td>
<td>JE</td>
<td>RS</td>
</tr>
<tr>
<td></td>
<td>JF</td>
<td>SG</td>
</tr>
</tbody>
</table>

Table 11.1. Reading speed change in each patient.
Figure 11.1. Change in reading speed for all AMD patients.

Table 11.2 below shows the magnitude of the mean deviation from the baseline reading speed at each visit for AMD and JMD patients.

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean deviation from baseline reading speed (words/minute)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 month</td>
</tr>
<tr>
<td>AMD</td>
<td>21</td>
</tr>
<tr>
<td>JMD</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 11.2. Mean deviation from baseline reading speed at each visit.

To ensure that the change in reading speed in patients is not attributable to regression to the mean, the magnitude of change in reading speed (|(change in reading speed -1)|) was plotted against baseline reading speed. There is no relationship between these two variables (r = 0.20; figure 11.2).
Examination of table 11.2 indicates that the level of change in reading speed is far greater in patients with AMD than in those with JMD. These two groups of patients are examined separately throughout this chapter.

11.1 Changes in reading speed for AMD patients

Stepwise multivariate analysis was applied in manner described in the previous chapter (section 10.1) using the variables shown in table 11.3. Change in these variables was used to predict change in reading speed over the course of the study.

Visual acuity and scotoma size were excluded from this analysis as they were by design invariant throughout the length of follow-up of the study.
### Variables entered into the multivariate model

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Dependent variable (Outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in fixation stability (log units)</td>
<td>Change in reading speed (exit/baseline)</td>
</tr>
<tr>
<td>Development of pseudofoveation (nominal variable; yes/no)</td>
<td></td>
</tr>
<tr>
<td>Development of a repeatable number of PRLs (nominal variable; yes/no)</td>
<td></td>
</tr>
<tr>
<td>Adoption of the “final” PRL (nominal variable; yes/no)</td>
<td></td>
</tr>
<tr>
<td>Change in saccadic latency (msec)</td>
<td></td>
</tr>
<tr>
<td>Change in saccadic efficiency (msec)</td>
<td></td>
</tr>
<tr>
<td>Change in saccadic velocity (°/sec)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 11.3.** Variables entered into the multivariate model.

The events described in the table above (development of pseudofoveation, development of a repeatable number of PRLs and adoption of the final PRL) were only classified as “yes” when they occurred between the entrance point and the exit point of the study; for example, patients who had already pseudofoveated at baseline would not be classed as developing pseudofoveation during the length of follow-up of the study.

#### 11.1.1 Change in reading speed between entrance and exit point for AMD patients

As figure 11.1 shows, reading speed changed by large amounts in some patients with AMD. The patient whose reading speed improved most over the length of the study was FG (exit reading speed = 1.95x baseline reading speed) whilst the poorest was JY (exit reading speed = 0.05x baseline reading speed). The mean exit reading speed was 0.91 times the baseline value (sd: 0.46). The distribution of change in reading speed is normally distributed (Shapiro-Wilk test, W=0.97, p=0.81).

Statistical regression indicated the presence of the same model when run forwards and when run backwards. A combination of three variables can predict change in reading speed to an $r^2$ value of 0.78. These factors were fixation stability, the development of a repeatable number of PRLs and the development of pseudofoveation (table 11.4).
### Table 11.4. Result of statistical regression. nPRL: number of PRLs.

<table>
<thead>
<tr>
<th>Step</th>
<th>Variable</th>
<th>Cumulative $r^2$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fixation stability</td>
<td>0.54</td>
</tr>
<tr>
<td>2</td>
<td>Development of repeatable nPRL</td>
<td>0.64</td>
</tr>
<tr>
<td>3</td>
<td>Development of pseudofoveation</td>
<td>0.78</td>
</tr>
</tbody>
</table>

There is no interaction between these three variables. The plot of the residual data from this model can be seen in figure 11.3.

![Figure 11.3. Plot of residual data for the model above.](image)

**11.1.2 Change in reading speed between 0 and 3 months for AMD patients**

Table 11.2 shows that the bulk of the change in reading speed occurs in the first three months after recruitment. To determine what factors account for this “early change” in reading speed, the variables in table 11.3 were entered into a stepwise model to predict the change in reading speed for the first three months after the development of the scotoma.

Mean reading speed at the three-month visit was 0.82 times the baseline value (sd:
The distribution of change in reading speed was normal (Shapiro-Wilk test, \( W=0.97, p=0.80 \)).

The stepwise model revealed that saccadic latency and saccadic efficiency are responsible for this "early change" in reading speed, to an \( r^2 \) value of 0.46. This model is described in table 11.5 below.

<table>
<thead>
<tr>
<th>Step</th>
<th>Variable</th>
<th>Cumulative ( r^2 ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Change in saccadic efficiency</td>
<td>0.34</td>
</tr>
<tr>
<td>2</td>
<td>Change in saccadic latency</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Table 11.5. Result of statistical regression.

There is no interaction between these two variables. The plot of the residual data from this model can be seen in figure 11.4.

![Figure 11.4. Plot of residuals for the "early change" model.](image)

11.1.3 Change in reading speed beyond 6 months for AMD patients

Examination of figure 11.1 shows that patients' reading speed appears to stay relatively stable beyond the six month visit. All of the patients whose ultimate reading speed was faster than their baseline reading speed had demonstrated this by
the six month follow-up visit. However, reading speed does deteriorate in some patients with AMD after the six month visit.

A further stepwise model was constructed to determine what factors account for this late deterioration in reading speed in some patients.

This model revealed that fixation stability change was the only predictive value for late changes in reading speed. Change in fixation stability was responsible for 67% of the variance in late changes in reading speed. This relationship is shown in figure 11.5.

![Graph](image_url)

**Figure 11.5.** Relationship between changes in fixation stability and reading speed in the “late phase” of the study. n=9.

### 11.1.4 Discussion

This section has used multivariate modelling techniques to predict the change in reading speed of patients over the course of this study.

Those patients whose fixation stability improves, who use a repeatable number of
PRLs and who pseudofoveate are the most likely to demonstrate an improvement in reading speed over the twelve months following the development of a scotoma. The magnitude of this improvement is not dependent on the baseline reading speed (figure 11.2).

The advantage of using a longitudinal design rather than a cross-sectional design for this study is that variance in intelligence, reading ability or other cognitive factors between patients are controlled to a large extent. However, as discussed in the previous chapter, this study has not controlled for change in motivation or any subsequent cognitive decline in our patients. This limitation will be addressed further in chapter 13.

It is perhaps surprising that reading speed deteriorates so markedly in some of the patients examined in this study, given that visual acuity and scotoma size is, by design, stable. One reason for this change may attributable to the fact that only the dense scotoma size has been measured in this study; those patients whose reading speed deteriorates may have exhibited a change in the relative scotoma size. It is tempting to speculate that a decrease in fixation stability is associated with an increase in the size of a relative scotoma size, which will account for the late changes in reading speed seen in some patients whose reading speed has previously been stable.

Early changes in reading speed have been defined as those which occur in the first three months following the development of a scotoma. Saccadic efficiency and latency are the best predictors of reading speed changes in this early phase of adaptation; patients whose saccadic latency lengthens and whose saccadic efficiency improves are the most likely to read more quickly. This is consistent with the research of McMahon and colleagues who found that immediately after a training programme, patients who had modified their saccadic efficiency demonstrated an improvement in reading speed. The data in this thesis also show that if fixation stability subsequently falls in patients, even those who have modified their saccadic efficiency, reading speed will deteriorate.

Interestingly there is no association between saccadic properties and the likelihood
of pseudofoveation (nominal logistic regression). This lack of association will be explored further in the general discussion section of this thesis.

After six months, reading speed is relatively stable. In the absence of visual acuity or scotoma size changes, fixation stability is the biggest predictor of reading speed change.

11.2 Changes in reading speed for JMD patients

As table 11.2 shows, the magnitude of change in reading speed for patients with juvenile forms of macular disease is smaller than that for the AMD patients seen in this study. There are two possible reasons for this. First, JMD patients may already have made the necessary adaptations by the time of their first assessment. Second, JMD patients may be less likely to make these adaptations than patients with age-related macular disease. Clinical intuition supports the first of these hypotheses.

If the first of these hypotheses is correct, patients with JMD will exhibit a similar pattern to AMD patients in the “late phase” of adaptation described above. Due to the small sample size in this group, stepwise regression is not appropriate. However, fixation stability is responsible for 32% of the variance in the change in reading speed exhibited by these patients. Adding pseudofoveation or the development of using a repeatable number of PRLs into this model does not significantly increase this $r^2$ value.

The differences between JMD and AMD patients will be discussed further in section 13.5 of the discussion chapter of this thesis.

11.3 Conclusion

An improvement in fixation stability, the development of pseudofoveation and the development of a strategy by which a repeatable number of PRLs is used are the most important factors in determining whether reading speed changes in patients with AMD. Together these factors account for nearly 80% of the variance in the
change in reading speed.

Immediately after the development of a scotoma, changes to the saccadic system are responsible for most of the changes in reading speed.

After six months, patients’ reading speed stays stable unless their fixation stability subsequently deteriorates. It is postulated that this change is secondary to a change in the size of the relative scotoma.

Although too few patients with JMD have been recruited for statistical comparison, the change in reading speed exhibited by these patients is more akin to the “late phase” changes made by AMD patients.

Why some patients develop the adaptive strategies which cause an improvement in reading speed whilst others do not will be explored in the next chapter of this thesis.
Chapter 12: Factors which predict successful rehabilitation to macular disease

Chapters 10 and 11 have shown that there is a wide range in patients’ reading speed and that reading speed changes in patients between their entrance and exit visits. This chapter will use statistical techniques to determine whether baseline characteristics determine how likely patients are to read fluently at the exit point from the study. In other words, is it possible to predict how well a patient will read after 12 months, based on results obtained immediately after the development of a scotoma?

Section 12.1 of this chapter will define the statistical terms used in this chapter. These terms include logistic regression, odds ratios and the receiver operating characteristic. Section 12.2 will assess which patients read at a fluent rate (faster than 80 words/minute) at the exit point of the study. Section 12.3 will determine which patients’ reading speed improves, or deteriorates, over the study. Section 12.4 is a general discussion of all of the findings of this chapter.

12.1 Specific methods

12.1.1 Logistic regression
Logistic regression is a statistical technique which allows the prediction of a discrete, nominal outcome on the basis of a set of variables which may be continuous, ordinal or nominal. For section 12.2 of this chapter, the outcome variable is an exit reading speed of faster than 80 words/minute. In section 12.3, two separate analyses have been performed. The first has an outcome variable of an improvement in reading speed of 27% or more between entrance and exit of the study. The second outcome is a deterioration in reading speed of the same amount over the same time scale.
12.1.2 Odds ratios

When the outcome variable in a logistic regression is a binary nominal variable, an odds ratio can be computed which indicates the likelihood of an outcome given the presence of the predictor. The formula used for this is:

\[
OR = \frac{N(\text{outcome } +\text{ve}, \text{ predictor } +\text{ve})}{N(\text{outcome } +\text{ve}, \text{ predictor } -\text{ve})} / \frac{N(\text{outcome } -\text{ve}, \text{ predictor } +\text{ve})}{N(\text{outcome } -\text{ve}, \text{ predictor } -\text{ve})}
\]

where \(N\) is the number of cases and \(OR\) is the odds ratio (Bland & Altman, 2000). The odds ratio indicates how likely an event is to occur over chance.

Where the predictor is a continuous variable, an interval size has to be used. The interval size determines the amount of change which is necessary for the probability to be increased by the given odds ratio. For example, if the interval size is 0.1 and the odds ratio is 2, then for every 0.1 change in the predictor variable, the odds of the outcome doubles (that is, it is twice as likely to occur).

12.1.3 The receiver operating characteristic

The receiver operating characteristic (ROC) plot is a way of determining to what extent results from a predictive test differ amongst subjects who do, or do not, have a positive outcome. The ROC plots sensitivity against 1 - specificity for every patient. The area beneath the ROC curve indicates the strength of a test: a perfect test would discriminate between all patients who have a positive outcome and all of those who do not, and the area beneath the curve would be 100% of the plot area. A test performing at chance would have an area beneath the curve of 0.50 (Altman & Bland, 1994a).

12.2 Prediction of which patients will read fluently at the study exit point

This section examines patients’ baseline characteristics and relates them to their reading speed at the exit point from the study. Demographic factors, clinical features and baseline reading speed have been used to predict the presence of fluent reading at the exit point of the study. Odds ratios have been calculated for each variable.
The minimum reading speed for fluent reading has been defined as 80 words/minute, after the work of Whitaker and Lovie-Kitchin (1991).

Table 12.1 shows the odds ratios (with 95% confidence intervals) for reading at greater than 80 words/minute at the exit point from the study.

<table>
<thead>
<tr>
<th>Demographic variables</th>
<th>Odds Ratio</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.0</td>
<td>0.96 - 1.03</td>
</tr>
<tr>
<td>Sex (being female)</td>
<td>0.54</td>
<td>0.22 - 1.33</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>Odds Ratio</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual acuity</td>
<td>1.08 (is: 0.1)</td>
<td>0.72 - 1.63</td>
</tr>
<tr>
<td>Contrast sensitivity</td>
<td>2.40 (is: 0.15)</td>
<td>1.13 - 5.07*</td>
</tr>
<tr>
<td>Scotoma size</td>
<td>0.42 (is: 1)</td>
<td>0.13 - 1.33</td>
</tr>
<tr>
<td>Having JMD</td>
<td>1.42</td>
<td>0.51 - 3.93</td>
</tr>
<tr>
<td>Having exudative AMD</td>
<td>1.42</td>
<td>0.55 - 3.63</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reading variables</th>
<th>Odds Ratio</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reading &gt;80 words/min at baseline</td>
<td>3.06</td>
<td>0.96 - 9.74</td>
</tr>
</tbody>
</table>

Table 12.1. Odds ratios for reading at more than 80 words/minute at the exit point from the study. is: interval size (odds per unit interval). *: statistically significant.

Odds ratios where the confidence interval includes 1 are not statistically significant. Thus contrast sensitivity is the only variable measured at baseline which significantly predicts whether patients will read fluently at the exit point from the study. Surprisingly, this is a better indicator than reading speed at the baseline visit.

Figure 12.1 shows the ROC plots for contrast sensitivity and baseline reading speed respectively. The area under the ROC plot is 0.84 for contrast sensitivity and 0.72 for baseline reading speed.
12.3 Predictive values for reading speed improving or deteriorating

Similar analyses were performed using two different outcomes; an improvement in
reading speed of 27% or more; or a deterioration by a similar amount. The results of
these analyses are shown in table 12.2.

<table>
<thead>
<tr>
<th></th>
<th>Improvement in reading speed</th>
<th>Deterioration in reading speed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>95% C.I.</td>
</tr>
<tr>
<td><strong>Demographic variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.18</td>
<td>0.08 - 12.6</td>
</tr>
<tr>
<td>Sex (being female)</td>
<td>0.71</td>
<td>0.24 - 2.09</td>
</tr>
<tr>
<td><strong>Clinical variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual acuity (is: 0.1)</td>
<td>0.88</td>
<td>0.54 - 1.43</td>
</tr>
<tr>
<td>Contrast sensitivity (is: 0.15)</td>
<td>1.24</td>
<td>0.71 - 2.16</td>
</tr>
<tr>
<td>Scotoma size (is: 1)</td>
<td>0.52</td>
<td>0.07 - 3.5</td>
</tr>
<tr>
<td>Having exudative AMD</td>
<td>1</td>
<td>0.08 - 12.6</td>
</tr>
<tr>
<td><strong>Reading variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reading &gt;80 words/min at baseline</td>
<td>0.95</td>
<td>0.33 - 2.78</td>
</tr>
</tbody>
</table>

Table 12.2. Odds ratios for an improvement or a deterioration in reading speed over
the course of the study. is: interval size (odds ratio per unit interval).

It was not possible to calculate odds ratios for an improvement or deterioration in
reading speed of patients with JMD as none of them demonstrated a change in
reading speed of this magnitude.
12.4 Discussion

The only significant predictor for reading fluently at the exit point of the study is to have a better contrast sensitivity. Age, sex, the type of disease, visual acuity, scotoma size and, most surprisingly, baseline reading speed do not predict the likelihood of fluent reading at the exit point of the study.

Baseline contrast sensitivity can predict the ability to read fluently at the exit point of the study. The area under the ROC plot for contrast sensitivity is 0.84. This indicates that if two patients are selected at random, one of whom reads fluently at the exit point and one of whom does not, there is an 84% chance that the one with the better contrast sensitivity will be the one which is able to read fluently (Bland & Altman, 1994a).

It can be seen from table 12.2 that it is impossible to predict whether a patient’s reading speed will improve or deteriorate based on any of the above variables measured at the baseline assessment. This finding is clinically encouraging in that it is possible for all AMD patients of any age, visual acuity or scotoma size to demonstrate an improvement in reading speed over the course of the study. An example of such a patient is FG, a 90 year old patient with a dense scotoma of 1 disc diameter and a presenting visual acuity of 0.6 logMAR. Over the course of the study, her reading speed improved from 44 to 87 words/minute.

The converse of this finding is that none of the factors described above (apart from having JMD) are protective against reading speed subsequently deteriorating. These findings will be discussed further in the general discussion chapter of this thesis.
Chapter 13: General discussion

This chapter will add to the specific discussion sections found in each results chapter and will discuss the principal findings of this study in relation to the hypotheses defined in the introduction. In particular, interactions between the results found in each chapter are explored. Limitations of the study are raised in each section and are discussed in section 13.6. The next chapter reports the clinical implications of this study and makes suggestions for future research projects.

13.1 Hypothesis 1: The development of the Preferred Retinal Locus

Hypothesis 1 of this thesis stated that:

"After scotoma development, patients will develop a consistent preferred retinal locus. The number of different PRLs used will reduce from many to one and fixation stability will improve. Patients will lose awareness of the use of the PRL."

The accuracy of this hypothesis is assessed in the following four subsections.

13.1.1 Development of a consistent PRL

The study presented in this thesis is the first to examine the timescale over which the PRL develops in patients with macular disease. The development of the PRL is remarkably quick; half of the patients examined in this study used the same PRL at their baseline assessment and at all subsequent visits; that is, a consistent PRL was used from the first attendance.

This thesis has shown that the location of the principal PRL changes in approximately half of the patients recruited into this study. At the exit point of the study, the distribution of PRL locations is similar to that found in cross-sectional studies such as those performed by Culham (1993), Sunness (1996) and Fletcher (1999). The results
presented in this thesis corroborate those of previous researchers who suggested that using a PRL above the scotoma (in visual field space) is suboptimal; all three patients who initially used a PRL in this location subsequently changed their PRL location.

For those patients who changed their PRL location, the median time taken was three months. All of the patients used their final PRL by the six month follow-up visit.

This study has corroborated the opinion of previous researchers that the location of the PRL does not affect reading speed (Sunness et al., 1996; Fletcher et al., 1999a).

The location of the final PRL appears to be idiosyncratic; as section 6.1.2.2 shows, there are no differences between patients who choose to use a PRL in the three locations in terms of visual acuity, scotoma size or disease type.

13.1.1.1 Do saccadic characteristics determine the final PRL location?

This study has measured more aspects of visual behaviour than many previous investigations into the location of the PRL. Post-hoc analysis was performed to determine whether the apparently idiosyncratic nature of the PRL location can be predicted by any other factors examined in this study, in particular saccadic efficiency.

Although there is no overall difference in saccadic efficiency in any particular direction (figure 8.4), within patients, performance was frequently better in one direction. To test the hypothesis that saccadic efficiency will determine the final PRL location, the direction of the most efficient saccades at baseline and the final PRL location was recorded for every patient. The most efficient saccades were those made towards the location of the final PRL in only 7/25 patients (35%). In those patients who changed their PRL location, baseline saccade efficiency predicted the location of the final PRL in only 4/12 patients (33%; no better than chance). This indicates that patients do not select their PRL based on the location to which the most efficient saccades are made.
13.1.1.2 What does predict the final PRL location?

None of the variables examined in this study can predict where the final PRL location of a given patient will be.

The scotometry performed in this study has only examined the extent of the dense scotoma and has not elicited the presence of any relative scotomas. One possibility is that patients place their PRL in the area of best functioning retina, regardless of its retinal position. This may explain why the PRL location changed in some patients; although their dense scotomas remained stable, the extent of the relative component of their scotoma may have changed. An experiment to contribute further knowledge to the debate over how patients select their final PRL is described later. The statement of Timberlake and colleagues, that “there appears to be no simple rule by which patients select a particular PRL”, is reinforced by the work in this thesis (Timberlake et al., 1987).

13.1.2 The number of PRLs used

The new quantitative techniques used in this thesis have enabled the number of PRLs to be determined more precisely than has previously been possible. Previous researchers have described multiple PRLs only when the loci are well separated (by at least 4° in Whittaker’s study; in different retinal quadrants in the study by Duret and colleagues (Whittaker et al., 1988; Duret et al., 1999)).

Chapter 7 of this thesis has shown that although the mean number of PRLs used by patients falls in some cases, a more pronounced change is that most patients develop a strategy of using a repeatable number of PRLs for each position of gaze. As figure 7.5 indicates, there is no advantage in reading speed in using one PRL rather than two. However, to use a repeatable number of PRLs is advantageous.

This work supports the opinion of Duret and colleagues that to use more than one PRL is not disadvantageous, as long as a strategy for using these multiple loci is employed.
Using multiple PRLs does not preclude the chance of pseudofoveation; there is no difference in the probability of pseudofoveating between those patients who use one locus and those who have multiple PRLs ($\chi^2=1.78$, $p=0.18$).

13.1.3 Fixation stability
This work has corroborated the well known finding that fixation stability is severely impaired in macular disease (chapter 7; Timberlake et al., 1987; Culham et al., 1993; Schuchard & Fletcher, 1994a; Rohrschneider et al., 1995).

The BCEA values recorded during this study are larger than those which have been found by other investigators, due to the different test conditions used for measuring fixation stability, as described in chapter 4. The method of assessing fixation stability used in this study provides a more realistic view of patients' natural fixational behaviour than previous studies have done; using a bite bar or other rigid head immobilisation techniques will suppress eye movements made to compensate for head motion.

There is a relationship between fixation stability and reading speed. This relationship has never previously been reported, although it has been suggested in a review paper by Schuchard (1994). Around 25% of the variance in reading speed can be accounted for by fixation stability; chapter 10 has shown that this variable has a significant role to play in the prediction of suprathreshold reading speed at both the entrance and the exit point from the study.

13.1.4 Awareness of PRL use
Chapter 6 has reported that some patients lose awareness of using their PRL, which has been defined as pseudofoveation. Sixteen (64%) of the patients made this adaptation during the year following scotoma development. Patients who made this adaptation read more quickly than those who do not pseudofoveate. Further, chapter 11 has shown that the development of pseudofoveation is associated with an increase in reading speed.

Contrast sensitivity, visual acuity and scotoma size do not predict the likelihood of
pseudofoveation. Similarly, characteristics of the PRL do not determine whether patients pseudofoveate (PRL location: logistic regression, p=0.33; fixation stability: Student’s t-test, p=0.55). Pseudofoveation does not occur until patients have developed their “final” PRL location; as figure 13.1 shows, there is a delay between finding the final PRL and losing awareness of PRL use. The median time between using the final PRL location and pseudofoveating is 5.5 months (IQR 0 – 11). Losing awareness of PRL use is, therefore, a later stage of PRL development than using a repeatable PRL location.

Figure 13.1. Time to find the final PRL compared to time to pseudofoveate. Line shows y=x.

13.1.5 Limitations
The scanning laser ophthalmoscope provides an excellent mechanism to assess fixation behaviour in macular disease. However, black-on-white text can not be presented using
the SLO, the field of view of the SLO is limited and patients have to view the screen from a fixed distance. For these reasons, reading performance was assessed in this study using a computer monitor and an infra-red gazetracker.

The major limitation of the latter technique is that the retina has not been viewed whilst patients have been reading. An assumption has been made that the same retinal location, and the same number of PRLs are used during the fixation task and whilst patients are reading. Even if the retina were imaged in this study, it would be very difficult to determine which retinal area is used for reading as it is not known where a patient is attending at any given moment. An experimental paradigm to address this problem has been discussed in chapter 14 of this thesis.

A further limitation of these results is that the interaction between the two eyes has not been assessed. Although the better eye has been assessed throughout this study, if the contralateral eye was strongly dominant then the patient might still use their worse eye to guide fixation (Schuchard et al., 1995). Recent experiments suggest that in patients with incongruous scotomas due to bilateral macular disease, a difference may exist in the fixation behaviour under monocular and binocular conditions (Kabanarou et al., 2003).

13.1.6 Conclusion
This section has shown that hypothesis 1 is partly correct. It is true to say that a consistent PRL develops after the onset of the scotoma, and that with time patients lose awareness of the PRL. However, fixation stability does not systematically improve and the number of PRLs does not fall from many to one.

13.2 Hypothesis 2: Changes in eye movements

Hypothesis 2 of this thesis stated that:

"The number of saccades used to locate a target will reduce over time. Foveating saccades will be suppressed and eye movements will be made directly to the PRL rather than to the scotoma. Eye movement control will
become more efficient when reading; with time, fewer saccades will be made to read a sentence, and the number of regressive saccades made during a reading task will fall.”

This hypothesis has been broken into three sections, each of which is discussed individually below.

13.2.1 Saccadic efficiency
Chapter 8 of this thesis has investigated the efficiency of saccades. A statistically significant increase in the number of saccades used by patients to observe a target was found, when compared to age-matched control subjects. All of the control subjects in this study located a target within 2 saccades, whilst patients used up to 4 saccades to complete the same task. Saccade efficiency improved in some patients, and by the exit point of the study eight patients (32%) reliably observed the target with two saccades or less.

This task was similar to that used by McMahon (McMahon et al., 1991; McMahon et al., 1993). McMahon also found that the number of saccades used to perform a task is doubled in patients with central scotomas when compared to individuals with normal vision.

13.2.2 Foveating and non-foveating saccades
This thesis has built upon the work of Stephen Whittaker in investigating foveating and non-foveating saccades (Whittaker et al., 1988; Whittaker & Cummings, 1990a; Whittaker & Cummings, 1990b; Whittaker et al., 1991). The introduction to Chapter 8 of this thesis has reviewed Whittaker’s work and defined non-foveating saccades as being those which are slower and display a longer latency than foveating eye movements. As discussed in chapter 8 (p. 141), saccadic latency has been used as the determinant of whether saccades are foveating or non-foveating.

Fifteen patients (60%) display non-foveating saccades at the exit point of this study. There is no difference between these patients and those who still make foveating
saccades in terms of visual acuity, scotoma size or diagnosis. These fifteen patients do not read any more quickly than those who do not make this adaptation (p=0.61).

13.2.3 Eye movements made whilst reading
The number of forward saccades used to read a sentence, the number of regressive saccades and the number of saccades used to find the start of a line are closely related at the baseline visit. At the baseline assessment, these variables are linearly related to the number of saccades used to view a target.

In some patients the number of saccades used to read a sentence falls. These changes are connected to an improvement in reading speed, but are not related to a change in other aspects of the saccadic system such as saccadic latency or efficiency. This lack of a transfer between the number of saccades used to find a target and the number of saccades used to read may explain why changes in saccadic properties are not a significant predictor of an improvement in reading speed over the course of this study.

Fixation duration has been found to be linearly related to reading speed in patients and in control subjects in this study. This relationship is similar to that previously described by Rayner (Rayner, 1978). Fixation duration remains unchanged over the course of this study.

13.2.4 Limitations
The major limitation of this section of the study is, once again, that the retina was not imaged during the saccadic assessment. The infra-red eyetracker was chosen to measure eye movements because of its high speed, to allow detailed assessment of saccade dynamics. An alternative approach would have been to use the SLO for the investigation of eye movements. This would have determined whether patients were truly making foveating or non-foveating eye movements, but would have reduced the accuracy of the latency and velocity measurements.

The ideal solution would be to have a system which enables retinal imaging, high-speed
eyetracking and full colour stimulus display. Possible solutions to this problem have been addressed in chapter 14.

13.2.5 Conclusion
Hypothesis 2 has been found to be partly correct. In some patients, the number of saccades used to locate a target reduced with time, whilst in other patients foveating saccades were suppressed. Eye movement control for reading became more efficient when reading in some patients.

13.3 Hypothesis 3: Prediction of reading speed

Hypothesis 3 states:

"The measurement of clinical, fixation and eye movement variables in this study will improve the prediction of reading speed in patients with central scotomas."

Chapter 10 of this thesis has used multivariate analysis to predict reading speed on the basis of clinical features and measurements made of fixation stability and eye movements. The model constructed is able to account for 68% of the variance in reading speed at baseline and 59% of the variance at the exit point of the study. Although these $r^2$ values are smaller than those of other researchers (table 10.1; (McMahon et al., 1993; Bullimore & Bailey, 1995; Bowers et al., 2001)), these previous investigators have all measured various parameters whilst patients are reading. This creates a classic cause and effect problem: it is impossible to determine whether the reduction in a variable (e.g. the number of letters per forward saccade) is a cause of slower reading speed, or a consequence of slower reading speed (Dowe, 1997). If parameters from the reading task are entered into the model, 87% of the variance in reading speed in this study can be accounted for.

13.3.1 Limitations
In common with all previous studies of this nature, a limitation to the modelling performed in chapter 10 is that the model has been created on the basis of a limited
number of patients. Although the effect of outliers has been controlled for to some extent by monitoring of outlying data and bootstrapping techniques, the only real way to validate this model is to apply it prospectively to another cohort of patients. It is possible that the patients recruited for this study may not be representative of the macular disease population as a whole. This concern is addressed further in section 13.6 below.

13.3.2 Conclusion
The results in this thesis have confirmed hypothesis 3, that the measurement of clinical, fixation and eye movement variables in this study improve the prediction of reading speed in patients with central scotomas.

13.4 Hypothesis 4: Functional performance will improve

Hypothesis 4 states:

"Reading performance will improve over time, in tandem with the improvements in fixation and eye movement control described above."

It can be seen from figure 11.1 that there is no systematic improvement in reading speed in the patients recruited into this study. Although this result is initially disappointing, it must be remembered that no training was incorporated into this study and that such intervention may improve reading speed in the remaining patients. The factors which influence absolute reading speed and changes in reading speed are described in chapters 10 and 11 and are shown in figure 13.2 overleaf.

Three factors were found to influence change in reading speed between the entrance and exit point of the study; an improvement in fixation stability, the development of a strategy by which patients use a repeatable number of PRLs, and non-awareness of PRL use. Together these strategies account for 78% of the variance in reading speed change. As some patients' reading speed deteriorates over the course of this study, these factors are also predictors for a deterioration in reading speed; an increase in fixation stability is
Figure 13.2. Factors which influence absolute reading speed and changes in reading speed in patients with AMD.

CROSS-SECTIONAL ANALYSIS (ABSOLUTE READING SPEED)

At baseline, limited by:
1. Saccade efficiency
2. Fixation stability
3. Scotoma size

At exit, limited by:
1. Fixation stability
2. Saccade efficiency
3. Contrast sensitivity

LONGITUDINAL ANALYSIS (CHANGE IN READING SPEED)

Early change: 0 to 3 months
Determined by saccadic changes

Overall change: 0 to exit
Determined by changes in fixation stability, using a repeatable number of PRLs and developing pseudofoveation.

Late change: 6 to 12 months
Determined by changes in fixation stability

associated with a decrease in reading speed.
13.4.1 The difference between “early” and “overall” change in reading speed

Figure 13.2 and chapter 11 indicate that the initial changes in reading speed, made over the first three months, are attributable largely to changes in saccadic properties. These factors are not included in the model which predicts change in reading speed at the exit point of the study. However, these early changes do not adequately predict exit reading speed; saccadic efficiency and latency are together responsible for only 18% of the variance in reading speed change over the course of the study. This implies that there are two separate phases to patients’ adaptation; early changes are determined by saccadic properties whilst later changes are determined by fixation characteristics. Of the two phases, the second phase is more significant in predicting patients’ ultimate reading speed.

13.4.2 The importance of fixation stability

Change in fixation stability is the most important variable in predicting change in reading speed over the timescale of this study. Further, it is the only factor which significantly affects reading speed after patients have suffered from macular disease for over six months. Examination of figure 13.2 shows that after six months, a deterioration in reading speed is more likely than an improvement. By design the patients who were included in the study beyond six months had stable lesions; the area of dense scotoma and visual acuity were unchanged. As previously discussed, the area of relative scotoma was not measured. It is possible that impairment in fixation stability is connected to an increase in the size of the relative scotoma. This limitation is discussed further below in section 13.4.5.

13.4.3 The importance of contrast sensitivity

Chapter 10 has shown that contrast sensitivity is more important than visual acuity, disease type or scotoma size in determining how quickly patients read at the exit point of the study. This reinforces previous descriptions of the importance of contrast sensitivity in predicting reading speed in patients with low vision (Legge et al., 1985a; Legge et al., 1985b; Legge et al., 1987; Rubin & Legge, 1989; Lawton et al., 1998).
Interestingly, contrast sensitivity is known to be related to subjective levels of impairment in low vision observers (Lennerstrand & Ahlstrom, 1989; McClure et al., 2000).

A reduction in contrast sensitivity may be related to the presence of a relative scotoma (Mitra, 1985). It is tempting to speculate that the level of contrast sensitivity impairment in this study is related to the size of any relative scotoma present. It would be interesting to know whether the area of the relative scotoma is as closely related to reading speed as contrast sensitivity is in this study. Unfortunately relative scotoma dimensions were not recorded in the present study.

Chapter 12 has shown that contrast sensitivity is the only measurement made at baseline which can predict whether patients will read fluently at the end of the study. Contrast sensitivity may precede an event which causes reading speed to become impaired; in geographic atrophy, contrast sensitivity is impaired before the foveal centre becomes atrophic (Sunness et al., 1995). Relative scotoma may precede the development of a dense scotoma from detachment of the sensory retina in patients with exudative AMD (personal communication, Professor A.C. Bird, London, 2004).

Seven patients were withdrawn from the study earlier than the scheduled end-point because of disease progression (see Appendix 1). Disease progression was determined as being a 0.2 logMAR change in visual acuity or an increase in the size of the dense scotoma. To determine whether low contrast sensitivity preceded progression of disease, an odds ratio was calculated with interval size 0.15. Baseline contrast sensitivity not predict an early exit from the study (OR: 0.91; 95% C.I.: 0.63-1.32). A change in contrast sensitivity does not appear to precede exit from the study (OR: 0.91 (95% CI: 0.50-1.66).

13.4.4 Other factors which predict an improvement in reading speed
The amount of reading which patients did at home was not measured in this study. Although patients who practise reading at home may be more likely to display an
improvement in reading speed, it is difficult to differentiate cause from effect: patients who notice that their reading speed has improved are far more likely to attempt to read a book or newspaper than those who do not.

13.4.4.1 Self-prescribed training
Although this thesis describes a natural history study which specifically excluded any training or other intervention, three patients reported that they did practice fixation tasks at home. PF reported that he practiced looking at the ends of beams on the ceiling (mimicking the saccade task in this study), JF practiced looking towards the red LED light on her television set and SG tried to make objects disappear by looking at them. Each of these patients volunteered this information without being asked so it may be that other patients behaved in a similar way at home but did not admit to this in the laboratory.

The tasks practiced by PF and JF are similar to saccade training tasks such as those used by McMahon and colleagues (McMahon et al., 1991; McMahon et al., 1993). SG's negative feedback training has not previously been described but is likely to detract from the likelihood of pseudofoveation so would not be recommended to others, based on the results of this thesis. Although it is impossible to statistically analyse whether these patients perform any better than those who do not train their visual behaviour at home (due to the small numbers involved and the fact that it is unknown whether other patients trained at home), it is worth noting that PF's reading speed improved by 27% over the course of this study, JF's stayed constant and SG's fell by 16%.

13.4.4.2 CCTV use
During a retrospective trawl of patients' notes, it was noticed that those who had a closed circuit television low vision aid (CCTV) appeared to be more likely to read quickly than those who did not. Post-hoc analysis did not reveal this effect to be statistically significant but there was a trend towards an increased likelihood of reading fluently at the exit point with CCTV use (odds ratio 2.66, 95% C.I. 0.73 – 9.71). This effect may be due to practice, rather than training. Further, those patients who are
capable of reading fluently are more likely to appreciate an improvement with a CCTV and therefore to purchase one.

13.4.4.3 Motivation
The Oxford English dictionary defines motivation as being “the general desire or willingness of someone to do something; drive, enthusiasm” (2nd edition, 1989). This description matches some of the patients in this study far more than others, and patients who appear to be more highly motivated appear to be more likely to demonstrate an improvement in reading speed than those who are not. Of course, in the context of this study, this observation is purely anecdotal. Although psychological instruments for determining motivation do exist, such as the Reiss profile (Reiss & Havercamp, 1998), they have not been applied in this study.

13.4.5 Limitations
The primary limitation of this analysis is that the area of relative scotoma was not recorded. It could be that the deterioration in reading speed experienced by some patients is a consequence of an increase in the size of the relative scotoma rather than any other adaptive strategies. This change would confound the models which have been created in chapter 11.

Measurement of relative scotomas using the scanning laser ophthalmoscope is a slow, fully manual procedure without the benefit of thresholding algorithms such as those developed for the Henson field analyser (Henson, 1993). To measure a dense scotoma manually in this patient group (using only one target intensity) took up to ten minutes. Manual mapping isopters of different target intensity would take far longer and would not be practical for the majority of the patients assessed in this study.

13.4.6 Conclusions
The first assumption of hypothesis 4, that reading speed will improve over time, has been rejected by the results presented in this thesis. However, reading performance changes, where they do occur, appear to be connected with changes in fixation stability
and eye movement control.

13.5 Hypothesis 5: Superior performance of patients with JMD

Hypothesis 5 of this thesis reads:

"Patients with juvenile macular disease will make the adaptations described in sections 1.7.3.1 and 1.7.3.2 above more quickly and more fully than will those with AMD."

13.5.1 Speed of adaptation

As chapters 6 and 7 have shown, the PRL appears to develop very quickly in patients with JMD. The median time for the JMD patients to pseudofoveate was one month, and all of the patients use a repeatable number of PRLs within three months.

JMD patients do not show significant changes in reading speed over the course of this study. As section 11.2 of this thesis has described, this implies that any adaptations have made immediately, by the time of their first laboratory assessment. The minimum time period between vision loss and initial assessment in this study was one week, due to the time required for patients to present, have a medical retina opinion, be informed about this study, give informed consent and attend the laboratory for baseline assessment. For some JMD patients this delay was two to three weeks. It was impossible, therefore, to assess whether the younger patients did make quick adaptive changes over these first three weeks. Unfortunately this delay is inevitable in this type of research.

13.5.2 Fullness of adaptation

All five of the patients with juvenile macular disease pseudofoveated and used a repeatable number of preferred retinal loci. In other regards, there are not differences in the adaptive strategies exhibited between the five JMD patients and the 20 AMD patients in this study. JMD patients are no more likely to read suprathreshold text fluently than their compatriots with AMD. Initially, this result is surprising and contradicts the author's clinical intuition gained by working in a low vision clinic for
several years. However, it must be remembered that reading speed has been assessed in this study when using magnified text on a monitor. Patients have not been required to use any low vision devices, to correctly position the text to be read, to adjust their viewing distance so that the text is in focus or to handle the controls on a CCTV. By eliminating these dexterity requirements, with which clinicians in low vision clinics are very familiar, patients with AMD are able to read just as quickly as those with JMD. This finding is of great importance and emphasises the need for well designed low vision aids and careful patient instruction in their use.

Rehabilitative outcomes of patients following sensory loss in other areas of medicine do not appear to be age dependent unless the impairment occurs in childhood. For example, in hearing loss secondary to noise exposure, impairment is not thought to be dependent on the age of onset (see (Syka, 2002) for a review). Similarly, the age of onset does not affect the rehabilitation of visual neglect following cortical lesions (Kerkhoff, 1998). It should not be surprising that patients with AMD are capable of reading just as fast as those with JMD.

13.5.3 Limitations
The number of patients recruited who suffered from juvenile forms of macular disease was smaller than was initially hoped. The major reasons for this were difficulty in identifying eligible patients due to the different mode of onset and the relative rarity of juvenile forms of macular disease. Understandably, some patients were unwilling to participate in this study due to their work, study or family commitments. The time at which patients were eligible for recruitment into this study was, of course, at a very stressful point in patients’ lives. For the same reasons, some JMD patients attended less frequently than the AMD patients.

13.5.4 Conclusion
This section has shown that there is evidence that JMD patients adapt more quickly than those with AMD do, but that there is no difference in the completeness of this adaptation. Hypothesis 5 of this thesis can not be confirmed on the basis of the research
carried out in this study.

13.6 Limitations of the study

Sections 13.1 – 13.5 of this chapter have described limitations of this study which are specific to the five hypotheses tested. This section will describe five further potential limitations of the study: how representative these results are of patients’ behaviour in the “real world”; whether the length of follow-up of this study is adequate; the onset of disease; possible enlargement of the relative scotoma; cognitive issues and psychological issues.

13.6.1 Relevance of the results

This study has only attempted to examine the visual behaviour of patients with central field loss caused by AMD, Stargardt disease or Best disease. The results of this thesis can not, therefore, be transferred to patients with other forms of macular disease such as macular hole or central serous retinopathy, or to those with traumatic macular damage such as that experienced by accidental laser injuries or solar burns. For example, the rehabilitation of a patient with laser injury has been reported to be far quicker (Zwick et al., 1998). It is likely that this difference can be attributed to the circumscribed nature of the lesion and the motivation of the patient.

The major outcome measure throughout this thesis has been reading speed. Reading was chosen as the outcome measure due to its importance, the frequency of patient complaints about being unable to read and its predictive value for performance on other tasks (Mangione et al., 1998; Wolffsohn & Cochrane, 1999; McClure et al., 2000).

Reading speed has been measured under nearly optimal conditions; text was presented one sentence at a time, at a large size and high contrast, on a computer monitor placed 50cm away from the patient. Only a simple reading addition was required to read these sentences. This task is far easier than most reading tasks which patients will perform
outside the laboratory such as reading a newspaper, checking shop prices or following a recipe book. This reading task was designed to remove the confounding effects of reading with low vision aids such as differences in the field of view between different devices, or practice in the use of magnifiers. However, patients were prescribed appropriate low vision devices at their baseline attendance and these LVAs were reviewed at each subsequent visit. It is entirely possible that some of the strategies which patients adopted were not of any benefit for the rather artificial task of reading sentences on a screen but were of use when reading with a magnifier. For example, some patients may have developed a "steady eye strategy" for reading with their LVA which was unhelpful when reading text on the monitor (Dickinson, 1998).

It is important to remember that few people spend the bulk of their time reading; especially amongst those with vision loss. It may be that patients have developed viewing strategies which are optimal for other tasks such as seeing facial expressions, watching television or navigation rather than for reading. No attempt was made in this study to determine whether patients' visual behaviour was optimised for reading or for another task. This would be an interesting subject for future research projects to investigate.

Mobility performance has been elaborately assessed in real and virtual environments under visual impairment by several researchers, such as Turano (Turano et al., 1998; Turano et al., 1999; Turano et al., 2001; Turano et al., 2002). An assessment of real world performance under binocular conditions was deemed to be beyond the scope of this thesis; however such assessment would have been of considerable interest.

13.6.2 Length of follow-up
This study has only assessed visual behaviour in the first twelve months following the development of a scotoma in each patient's second affected eye. The location of the PRL at the exit point from this study matches those results found by cross-sectional studies of visual behaviour in macular disease (see table 6.4). This suggests that by the end of this study, patients are displaying their final PRL location. Although
pseudofoveation does not occur in all patients within the course of this study, in those patients where this adaptation is made, it occurs within six months. The proportion of patients which have made this adaptation in this study (67%) is similar to that described in previous studies (86%; White & Bedell, 1990). Further, the proportion of patients using multiple PRLs at the exit point of this study (44%) is very similar to the proportion found by Whittaker (39%, (Whittaker et al., 1988). These findings imply that, from the point of view of the development of the PRL, the length of follow-up for this study is appropriate.

Saccadic properties of the patients seen in this study do not exactly match those of previous researchers. At the exit point of this study 15 patients (60%) appeared to be making non-foveating saccades (see chapter 8). A higher proportion of patients used non-foveating saccades in the studies by White (95%, White & Bedell, 1990) and by Whittaker (94%, Whittaker et al., 1991). The one patient in Whittaker’s study who did not make non-foveating saccades had only a 12-month history of macular disease. It may be that if the patients in this study were followed up for longer then their saccadic system may adapt further.

Seven of the patients in this study were removed from the study before the end of their planned follow-up due to deterioration in their macular disease. The findings of this study are contingent on the disease remaining stable. Therefore, the benefits of lengthening a longitudinal study of this nature would be in part counteracted by the reduction in the number of patients who would still exhibit unchanged macular disease.

13.6.3 The onset of disease
Patients have been recruited when they reported that their vision deteriorated and attended the hospital. The time of recruitment is, therefore, dependent on each patient’s individual judgement of when their disease worsened rather than by any objective measure of the onset of disease. In some instances patients had not attended the hospital for many years prior to the visit leading to their recruitment for this study. It is unknown whether these patients had any evidence of macular disease before their
attendance. Strictly speaking, this study has reported visual adaptation to a visual event (being a sudden decrease in vision) rather than the onset of macular disease.

The only way to overcome this would be by repeated visits of patients with a macular lesion in one eye, where the healthy eye could be assessed until the disease process became apparent. Such a study design would require a very large expense of time on the part of patients and investigators.

13.6.4 Potential enlargement of the area of relative scotoma

The possibility of the relative scotoma enlarging during the course of this study has already been referred to. If the relative scotoma increases in the absence of an absolute scotoma enlargement, a reduction in performance on contrast sensitivity and fixation stability would be expected. If the enlargement was sufficiently great, PRL location and the presence pseudofoveation may also change. As no patients in this study experienced a change in PRL location after 6 months or went from pseudofoveating to non-pseudofoveating, it appears unlikely relative scotoma has increased by a large extent.

13.6.5 Cognitive factors

No attempt has been made to control for cognitive decline over the course of the study. Given the age of many of the participants, it is feasible that changes in reading speed may be unrelated to visual factors, but actually be caused by a change in a patient’s neurological condition. Although all of the patients were apparently cognitively intact throughout the period of this study and did not have any diagnosed neurological disease, formal assessment of their cognitive function at each visit would have been of benefit.

13.6.7 Psychological factors

The patients assessed in this study all chose to participate and were consequently sufficiently motivated to attend the laboratory repeatedly. The incentives given of having frequent LVA reassessment is also likely to appeal more to those patients who are likely to read frequently at home than to patients whose interests are less cerebral. Although education was not formally assessed, anecdotally, the patients were more
highly educated than many patients seen in ophthalmology clinics; several held higher
degrees and nearly all worked in the professions. The results reported in this thesis may
not be transferable to patients who were less enthusiastic about reading.

Section 1.2.3.1 of the introduction to this thesis has discussed the psychological
adaptation of patients to visual loss. An inevitable consequence of a study which
recruits patients as they report second-eye visual impairment is that they will be at the
initial stage of the grieving process. Over the course of twelve months they would be
expected to reach the stage of acceptance to their visual loss. Psychological adaptation
may confound the visual rehabilitation which this study aims to identify.

13.7 Meeting the aims of the study

Section 1.7.3 of this thesis described the aims of the study. This section will briefly
review these three aims and will assess how fully this thesis has addressed them

13.7.1 Aim 1

The first aim of the study was “to examine and quantify the adaptive strategies which
are naturally adopted by patients who have lost central vision due to macular disease,
with particular reference to fixation behaviour, the number of preferred retinal loci used
and the use of non-foveating saccades.” Fixation and saccade behaviour have been
measured using sophisticated instruments, whilst a novel technique has been developed,
validated and applied to objectively determine the number of loci used for fixation. No
intervention has been used, to determine the natural history of these adaptive strategies.

13.7.2 Aim 2

The second stated aim of this study was “to determine the changes in these adaptive
strategies which occur for a period of twelve months immediately following visual loss
in the second eye to lose central vision.” This study has addressed this aim by
recruiting patients immediately after a significant drop in their perceived central vision
in the second eye to be affected by macular disease, and by following patients for this length of time.

13.7.3 Aim 3
Aim 3 was “to determine the relative utility of each of these adopted strategies, with particular reference to reading speed and change in reading speed.” Reading speed has been carefully measured at each visit and multivariate statistical techniques have been used to model the relative importance of these adaptive strategies in terms of absolute reading speed and change in reading speed.
Chapter 14: Clinical implications and suggestions for future research

This chapter will discuss the implications of the work presented in this thesis for clinicians working in low vision and ophthalmology clinics. It will also suggest future research projects to answer some of questions which this thesis has raised.

14.1 Clinical implications

The clinical implications of this thesis can be grouped into three major categories; advice for counselling patients with macular disease, practice in low vision clinics and suggestions for the development of training programs.

14.1.1 Implications for low vision assessment and counselling patients with AMD

An important finding of this thesis is that it appears patients with AMD are able to read just as well as those with JMD. This finding contradicts the experience of many practitioners working in low vision clinics. Section 13.5 of this thesis has discussed how this difference may be attributable to the handling of low vision devices. This reinforces the importance of patient education in the use of low vision aids, as well as the necessity for good ergonomic design.

The importance of contrast sensitivity in determining reading speed was described in chapter 12 and section 13.4.3. It is suggested that measurement of contrast sensitivity should be an integral part of every low vision assessment to gain a more complete understanding of the level of impairment which patients with macular disease experience.

This thesis has shown that some patients with relatively poor visual acuity and large scotomas managed to read fluently at the exit point of this study. The results of this thesis suggest that patients should not be too despondent if their reading speed at
presentation is relatively poor, as in certain patients reading speed improves markedly over the following six months. As always, practitioners should avoid giving patients false hope; reading speed does deteriorate in a large proportion of patients.

Figure 13.2 illustrates that some patients experienced dramatic changes in their reading speed over the course of the study. This has important implications for the provision of LVAs for patients; the device selected for a patient at their baseline visit will not necessarily be the correct device after six months. In this study LVAs were reviewed at each patient visit. Anecdotally, several patients were prescribed devices with lower magnification at subsequent visits, implying that as the adaptive processes described here develop, less magnification is required to perform a task. It is therefore suggested that all patients seen in the low vision clinic are offered review appointments after they have adapted to their visual loss.

14.1.2 Training visual behaviour
Section 1.6 of the introduction to this thesis introduced three training programs for patients with macular disease; training awareness of the PRL location; teaching the use of an “optimal” PRL and teaching eye movement control.

The method of training awareness of the PRL location, as advocated by Holcomb & Goodrich (1976) and by Shuchard and colleagues (1994), is not supported by the results presented in this thesis. Conversely, chapter 6 of this thesis has shown that non-awareness of the PRL is of benefit in determining which patients read quickly at the exit point of this study. This result indicates that training awareness of the PRL may be counterproductive in this group of patients.

Chapter 6 of this thesis has found that the location of the PRL is not related to reading speed at either the baseline assessment or the exit point of the study. This finding has corroborated work by other groups (Sunness et al., 1996; Fletcher et al., 1999b). This finding does not directly support training systems which encourage patients to use an alternate PRL, such as those described by Goodrich or Nilsson (Goodrich et al., 1985;
Nilsson et al., 1998). However, Culham and colleagues have shown similar techniques to improve fixation stability (Culham et al., 1997). This may explain, in part, the reading speed improvement described by these groups.

According to the results of this thesis, teaching eye movement control in the manner described by McMahon (1993) is the training system most likely to be of use in this patient group. Chapter 8 has shown saccadic efficiency to be related to reading speed, and McMahon's patients demonstrated an improvement in both saccade efficiency and reading speed. However, chapter 11 has shown that although saccadic properties are responsible for short-term changes in reading speed, fixation stability remains of more importance for long-term reading speed improvements.

An alternative method to training better eye movement control is to teach patients to use the steady eye strategy whereby text is moved (either by being scrolled electronically or by the patient moving the page) whilst the eye remains static. Assessment of reading in this method can help to quantify the amount of benefit which can be gained by developing optimal eye movement strategies.

14.1.2.1 An "ideal" method for training visual behaviour in patients with MD?

Chapter 11 has shown that the factors which are of most importance in predicting a long-term increase in reading speed are fixation stability, using a repeatable number of PRLs and fixation stability. Further, chapter 10 has shown that saccadic efficiency is of importance in determining patients' absolute reading speed.

The results of this thesis suggest that the most useful training program may involve tasks which improve fixation stability, which train patients to use a repeatable number of PRLs, and which train patients to ignore the fact that they are using a PRL. A suitable task may be to follow a target on a screen which progressively gets smaller (so that more precise fixation is needed to identify it). This system would also train saccade efficiency. Although saccade efficiency has not been shown to improve reading speed over the course of the study, it is of importance in the early stage of rehabilitation.
Further, saccadic efficiency is a predictor of a high absolute reading speed (chapter 10).

Of course, such a training scheme would need extensive development and validation before being introduced into clinical practice.

**14.2 Suggestions for future research**

**14.2.1 The efficacy of training**

A logical extension to this study is to investigate whether practitioner intervention can improve patients' adaptation to central vision loss. Several research groups have documented that reading speed or other measures of visual performance can improve with training, using a variety of methods (section 1.6, Goodrich & Mehr, 1986; Nilsson & Nilsson, 1986; McMahon et al., 1993; Nilsson et al., 1998). A limitation of many previous studies in this area is the lack of control groups who receive equal contact time with a health care professional. Patient motivation could well be a confounding factor; those who are most highly motivated to read again are more likely to attend multiple training sessions and to practice at home.

It is important to dissociate training from practice effects. Training is reserved for programs by which patients receive feedback, whereas practice is repetition of a task without feedback (Chung et al., 2004).

The ideal experiment to address the success of training of visual behaviour would be of a double-masked design. Patients would be randomly assigned to a treatment and a control group, with stratification based on their disease type, visual acuity and ideally motivation (as assessed by a psychological instrument). Both the treatment and control groups would have equal amounts of clinic time and would have "homework" to perform. In the treatment group the contact time would involve task training and the homework would be to perform, for example, training of eye movements. The control group would have contact time with a rehabilitation worker and would be asked to use
the "Learn to use your vision for reading" workbook (LUV workbook) at home. The LUV workbook consists of reading tasks which get progressively more difficult (Watson et al., 1992; Wright & Watson, 1995). Reading speed would be assessed at various stages by investigators who would be masked as to the group allocation of each patient.

14.2.2 Fixation assessment during reading

As section 13.1.5 has described, a limitation of this study is fixation behaviour was not monitored with the SLO whilst patients were reading. The eyetracker was used for reading assessment due to its larger field of view, higher stimulus quality and free-head nature.

Equipment modifications could overcome some of these difficulties. Combining three lasers, with long, medium and short wavelengths within the visual spectrum could enable the production of full-colour stimuli. Using this technique may allow black-on-white text to be produced, although the problem of artefacts appearing within the raster from curved letters would need to be addressed (Culham et al., 1992). Unfortunately such a system has not been sufficiently developed (Personal communication, Prof. F. Fitzke, London, 2003). A simpler equipment modification would be to use a semi-silvered mirror to reflect stimuli from a computer monitor onto the viewing axis of the SLO. This technique was applied in the validation experiment described in section 4.1. Unfortunately the contrast of the stimulus was reduced and it was decided not to use this approach for the current study.

Even if these technical problems are overcome, it is very difficult to know which retinal area a patient is using for reading at any given time. As a delay exists between attending a word and reading aloud, patients are not necessarily attending to the retinal area corresponding to the location of the word at the time when they read it aloud. This is particularly acute when more than one PRL is employed. A way of overcoming this would be to present a sentence of prose with words changing every few milliseconds (fig 14.1). Any combination of the four words would make some sort of sense. If
patients are asked to read aloud, the retinal location which corresponds to the word read when it was displayed must be that used for reading.

0 msec: Mark’s car doesn’t start
100 msec: Mike’s cat isn’t asleep
200 msec: Mick’s dad hasn’t eaten
300 msec: Matt’s dog wasn’t clean

Figure 14.1. Text which could be presented on the SLO to determine which retinal area is used for reading.

14.2.3 Assessment of the choice of PRL location
Despite the detailed analysis performed in this thesis, it is still not clear why there is no systematic location for the patients’ final PRL location. It is still unknown whether the PRL is selected because it is in the best functioning area of remaining retina or whether performance at the PRL is better because of practice in its use. Objective techniques such as electroretinography could be used to determine retinal performance at the PRL and at an equally eccentric non-preferred retinal location. The results of these tests would indicate whether retinal considerations predict the location of the PRL or whether other factors are of more importance.

14.2.4 The role of cortical adaptation to macular disease
The recent development of imaging techniques such as functional magnetic resonance imaging (fMRI) provides an exciting mechanism for assessing cortical changes associated with macular disease. In particular, the differences in activity in primary visual cortex between those patients who adapt successfully to AMD and those who do not would be of great interest.

14.2.5 Conclusion
Although this thesis has investigated the development of the PRL and other adaptive strategies in some detail, there are many questions which remain unanswered. Only with careful experimental design, elaborate equipment and a large supply of willing patients can further research be performed to answer the question posed in the first
paragraph of this thesis: why do patients with apparently identical clinical features exhibit very different levels of impairment?
Chapter 15: Conclusions

This thesis has described the first longitudinal study to investigate the development of viewing strategies in patients with newly presenting macular disease. The major conclusions of this study are described below.

15.1 The preferred retinal locus (PRL)

This thesis has shown, for the first time, the timescale over which the preferred retinal locus develops. The PRL is selected very early in the rehabilitative process; within two weeks of scotoma development in many cases and within six months in all cases. The reasons which patients have for selecting one PRL location over another remain mysterious. Many patients become unaware that they are using a PRL rather than viewing objects directly. This unawareness is beneficial in terms of rehabilitation.

Application of sensitive tests for the number of retinal loci has helped to determine that some patients use more than one fixation locus for a task. There is no difference in performance between patients who use one PRL and those who use two PRLs. However, patients who repeatably use the same number of loci read more quickly than those who do not have such a strategy.

Fixation stability does not change by large amounts over the course of this study. However, these small changes in fixation stability, in conjunction with other adaptive strategies, are important in determining change in patients’ reading speed.

15.2 Eye movements

Using high-speed eyetracking, two adaptive strategies of the saccadic system have been identified; an improvement in saccadic efficiency (that is, a reduction in the number of saccades used to perform a task) and the adoption of non-foveating saccades. These
two strategies occur independently of each other. These adaptations to the saccadic system are responsible for 46% of the variance in reading speed change experienced by patients in the first three months after their vision loss, although in the long term these strategies do not affect the change in reading speed.

Saccade efficiency is an important determinant of absolute reading speed in patients throughout this study.

15.3 Reading performance

Reading speed is significantly slower in those with macular disease than in age-matched control subjects. The level of this impairment can be predicted by taking into account patients’ saccadic efficiency, fixation stability, scotoma size and contrast sensitivity. The only variable measured at the baseline assessment which can predict whether patients are able to read fluently (at more than 80 words per minute) at the exit of the study is contrast sensitivity.

Over the course of this study, reading performance improved in four patients (16%), deteriorated in 7 patients (28%) and remained constant in the remaining 14 patients. Factors which determine an improvement in reading speed are changes in fixation stability, losing awareness of using the preferred retinal locus and using the same number of PRLs for different tasks.

15.4 Prediction of which patients rehabilitate well

It was not possible to predict which patients will exhibit an improvement in reading speed over the first year after developing macular disease, and in which patients reading speed will deteriorate. In particular, there are no differences in the performance of AMD and JMD patients at the exit point of this study. Under ideal conditions, patients with AMD can read just as fast as their younger counterparts.
References


Appendix 1: Patient characteristics, attendances and data

Tables A1.1 to A1.4 describe demographic factors, diagnosis and attendances for each patient. In the instance of early removal from the study, the reason for this is given. Tables A1.5 onward give raw data for the results presented in each chapter.

A1.1 Age-related macular disease group

<table>
<thead>
<tr>
<th>Initials/sex/age</th>
<th>Diagnosis in study eye</th>
<th>Baseline date</th>
<th>Discharge point, reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>FG/F/90</td>
<td>Exudative AMD</td>
<td>07/12/01</td>
<td>12 months</td>
</tr>
<tr>
<td>KD/F/76</td>
<td>Geographic AMD</td>
<td>14/12/01</td>
<td>12 months</td>
</tr>
<tr>
<td>RS/F/60</td>
<td>Geographic AMD</td>
<td>04/02/02</td>
<td>6 months, disease progression</td>
</tr>
<tr>
<td>MA/F/81</td>
<td>Exudative AMD</td>
<td>15/03/02</td>
<td>12 months</td>
</tr>
<tr>
<td>EC/M/81</td>
<td>Exudative AMD</td>
<td>07/06/02</td>
<td>18 months</td>
</tr>
<tr>
<td>AS/F/75</td>
<td>Geographic AMD</td>
<td>17/06/02</td>
<td>12 months</td>
</tr>
<tr>
<td>DB/M/73</td>
<td>Exudative AMD</td>
<td>02/07/02</td>
<td>12 months</td>
</tr>
<tr>
<td>PF/M/78</td>
<td>Exudative AMD</td>
<td>15/07/02</td>
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</tr>
<tr>
<td>JW/F/75</td>
<td>Geographic AMD</td>
<td>02/08/02</td>
<td>18 months</td>
</tr>
<tr>
<td>JM/F/55</td>
<td>Exudative AMD and myopic maculopathy</td>
<td>03/09/02</td>
<td>6 months, disease progression</td>
</tr>
<tr>
<td>JY/F/71</td>
<td>Exudative AMD</td>
<td>23/09/02</td>
<td>6 months, disease progression</td>
</tr>
<tr>
<td>JF/F/87</td>
<td>Exudative AMD</td>
<td>07/10/02</td>
<td>6 months, disease progression</td>
</tr>
<tr>
<td>SG/F/73</td>
<td>Exudative AMD</td>
<td>18/10/02</td>
<td>12 months</td>
</tr>
<tr>
<td>CA/M/78</td>
<td>Exudative AMD</td>
<td>08/11/02</td>
<td>12 months</td>
</tr>
<tr>
<td>BN/F/56</td>
<td>Geographic AMD</td>
<td>18/11/02</td>
<td>6 months, disease progression</td>
</tr>
<tr>
<td>IP/F/75</td>
<td>Exudative AMD</td>
<td>22/11/02</td>
<td>3 months, disease progression</td>
</tr>
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<td>RH/M/84</td>
<td>Exudative AMD</td>
<td>26/11/02</td>
<td>12 months</td>
</tr>
<tr>
<td>HP/M/84</td>
<td>Exudative AMD</td>
<td>03/12/02</td>
<td>6 months, disease progression</td>
</tr>
<tr>
<td>RG/M/76</td>
<td>Exudative AMD</td>
<td>20/01/03</td>
<td>12 months</td>
</tr>
<tr>
<td>BP/F/75</td>
<td>Exudative AMD</td>
<td>14/03/03</td>
<td>6 months, poor general health</td>
</tr>
</tbody>
</table>

Table A1.1. Characteristics of AMD group. Age is in years and at the time of recruitment. Discharge point is the time, after baseline, of the last attendance. Disease progression is defined as a VA drop of more than 2 lines or an increase in scotoma size of 1 disc diameter or more.
### A1.2 Age-matched subjects for AMD group

<table>
<thead>
<tr>
<th>Initials/sex/age</th>
<th>Baseline date</th>
<th>Discharge point</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR/F/72</td>
<td>25/03/02</td>
<td>12 months</td>
</tr>
<tr>
<td>BR/M/71</td>
<td>25/03/02</td>
<td>12 months</td>
</tr>
<tr>
<td>JC/F/80</td>
<td>15/10/02</td>
<td>12 months</td>
</tr>
<tr>
<td>TW/M/75</td>
<td>18/02/03</td>
<td>12 months</td>
</tr>
<tr>
<td>JH/F/72</td>
<td>7/03/03</td>
<td>12 months</td>
</tr>
</tbody>
</table>

Table A1.2. Characteristics of subjects without macular disease, age-matched for AMD group

### A1.3 Juvenile macular disease group

<table>
<thead>
<tr>
<th>Initials/sex/age</th>
<th>Diagnosis in study eye</th>
<th>Baseline date</th>
<th>Discharge point, reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP/M/44</td>
<td>Stargardt disease</td>
<td>16/11/01</td>
<td>12 months</td>
</tr>
<tr>
<td>CT/F/17</td>
<td>Best disease</td>
<td>10/09/02</td>
<td>12 months</td>
</tr>
<tr>
<td>JA/F/35</td>
<td>Stargardt disease</td>
<td>28/10/02</td>
<td>6 months, lost to follow-up</td>
</tr>
<tr>
<td>JE/M/17</td>
<td>Stargardt disease</td>
<td>28/03/03</td>
<td>6 months</td>
</tr>
<tr>
<td>MF/F/33</td>
<td>Stargardt disease</td>
<td>17/03/03</td>
<td>6 months</td>
</tr>
</tbody>
</table>

Table A1.3. Characteristics of subjects with early-onset macular disease. Subject JA moved out of the area and was lost to follow-up.

### A1.4 Age-matched subjects for JMD group

<table>
<thead>
<tr>
<th>Initials/sex/age</th>
<th>Baseline date</th>
<th>Discharge point</th>
</tr>
</thead>
<tbody>
<tr>
<td>PB/M/36</td>
<td>12/11/02</td>
<td>12 months</td>
</tr>
<tr>
<td>AG/F/33</td>
<td>02/12/02</td>
<td>12 months</td>
</tr>
<tr>
<td>GH/M/24</td>
<td>27/01/03</td>
<td>12 months</td>
</tr>
</tbody>
</table>

Table A1.4. Characteristics of subjects without macular disease, age-matched for JMD group
### A1.5 Data for chapter 5

This table gives the baseline data for all patients as used in chapter 5.

<table>
<thead>
<tr>
<th>Initials</th>
<th>Group</th>
<th>ETDRS</th>
<th>CS</th>
<th>NVA</th>
<th>SS</th>
<th>RS</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP</td>
<td>J</td>
<td>0.7</td>
<td>0.15</td>
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<td>0</td>
</tr>
<tr>
<td>AS</td>
<td>A</td>
<td>0.72</td>
<td>1.2</td>
<td>20</td>
<td>1.5</td>
<td>34</td>
</tr>
<tr>
<td>BN</td>
<td>A</td>
<td>0.7</td>
<td>0.95</td>
<td>12</td>
<td>0.5</td>
<td>77</td>
</tr>
<tr>
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<td>A</td>
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<td>0.75</td>
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</tr>
<tr>
<td>CA</td>
<td>A</td>
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<td>1.05</td>
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</tr>
<tr>
<td>EC</td>
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<td>10</td>
<td>1.5</td>
<td>129</td>
</tr>
<tr>
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<td>0.56</td>
<td>1.2</td>
<td>10</td>
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<td>1.35</td>
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<td>136</td>
</tr>
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<td>20</td>
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<td>96</td>
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</tr>
</tbody>
</table>

**Table A1.5.** Baseline information for all patients. Group: A=AMD, J=JMD; ETDRS: Distance visual acuity (logMAR units); CS: Contrast sensitivity (log units); NVA: Near visual acuity (N units); Scotoma size (disc areas); RS: Reading speed for suprathreshold text (words/minute).
## A1.6 Data for chapter 6

This table gives the data used for the PRL location and awareness of PRL use discussed in chapter 6.

<table>
<thead>
<tr>
<th>Initials</th>
<th>Group</th>
<th>PRL baseline</th>
<th>PRL exit</th>
<th>PRL change?</th>
<th>Re-ref?</th>
<th>Re-ref time</th>
<th>RS baseline</th>
<th>RS exit</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP</td>
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<td>R</td>
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<td>N</td>
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</tr>
</tbody>
</table>

Table A1.6. PRL location, re-referencing and reading speed data for all patients.  
Group: A=AMD, J=JMD; PRL baseline: PRL location in visual field space at baseline; PRL exit: PRL location in visual field at exit; PRL change?: PRL location change over course of study, Y=Yes, N=No; Re-ref?: Re-referencing occurs over the course of the study, Y=Yes, N=No; Time to re-ref: Time in months for re-referencing to occur; RS baseline: reading speed at baseline (words/minute); RS exit: reading speed at exit (words/minute).
### A1.7 Data for chapter 7

This table gives the data used for the fixation stability and the number of PRLs used location discussed in chapter 7.

<table>
<thead>
<tr>
<th>Initials</th>
<th>FS baselining</th>
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<th>logFS exit</th>
<th>nPRL base</th>
<th>nPRL exit</th>
<th>RepPRL base</th>
<th>RepPRL exit</th>
<th>multPRL base</th>
<th>multPRL exit</th>
</tr>
</thead>
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</tr>
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Table A1.7. Fixation stability, number of PRLs and repeatability of number of PRLs for all patients. FS baseline: fixation stability at baseline (BCEA, minarc²); logFS base: natural logarithm of fixation stability at baseline (log minarc²); logFS exit: natural logarithm of fixation stability at exit (log minarc²); nPRL base: mean number of PRLs used at baseline; nPRL exit: mean number of PRLs used at exit; repPRL base: the use of a repeatable number of PRLs at baseline (y=yes, n=no); repPRL exit: the use of a repeatable number of PRLs at exit (y=yes, n=no); multPRL base: the use of multiple PRLs at baseline (y=yes, n=no); multPRL exit: the use of a repeatable number of PRLs at exit (y=yes, n=no).
A1.8 Data for chapter 8

This table gives the saccadic data for each patient at each visit. Missing data is caused by random failure of the eyetracker. Where all saccade data is missing from a visit, the row has been deleted.

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### A1.9 Data for chapter 9

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M.D. Crossland. Appendix 1: Patient characteristics and data

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**Table A1.9 (and previous page).** Reading saccade data for all patients at each visit. Visit: (months); F sacc: mean number of forward saccades to read the sentence; Reg sacc: mean number of regressive saccades per sentence; Start sacc: mean number of saccades to the start of each line; FD: fixation duration (msec); RS: suprathreshold reading speed (words/minute).
Appendix 2: Patient information booklet and consent form

The following pages show the patient information booklet which was read by all participants, and the consent form which was signed prior to data collection starting.
VISUAL BEHAVIOUR IN MACULAR DISEASE:
PATIENT INFORMATION BOOKLET
AND CONSENT FORM

Please read this booklet carefully.
If you are unable to see the text, or if there is anything you do not understand, please ask a member of the study team for their help.

You are being invited to take part in a research study. Before you decide if you want to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with your friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Consumers for Ethics in Research (CERES) publish a leaflet entitled “Medical Research and You.” This leaflet gives more information about medical research and looks at some questions you may wish to ask. A copy may be obtained from CERES, PO Box 1365, London N16 0BW.

Thank you for reading this.
What is the purpose of the study?

People with macular disease are often unable to see with the central part of the vision. However, the peripheral ("side") vision is usually good. Therefore some people with macular disease look at things with their side vision rather than by looking straight at them. The goal of this study is to find out how people with different types of macular disease learn to use their side vision for everyday tasks like reading and recognising faces.

Why have I been chosen?

You have been chosen for this study by your doctor because you have a particular type of macular disease and your vision has recently changed. Around 40 patients in your situation have been chosen for the study.

Do I have to take part?

It is up to you to decide whether or not you want to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you do decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive. [If you do not wish to take part in this study you will not be at a disadvantage and will continue to receive normal clinical management.]

What will happen to me if I take part?

You will be asked to come to the Institute of Ophthalmology (next to the main part of Moorfields Eye Hospital) up to 5 times over the next year. The visits are more frequent in the first stages of the study because your use of "side vision" will be changing at this time.

Each visit will last about an hour. During each visit, some or all of these tests will be done:

- Refraction (a normal eye test)
- Measurement of your vision and reading will be tested using different charts
• A special instrument called an SLO will be used to look at the back of the eyes. You will be asked to look at different letters, shapes or words which will be shone into your eye by the machine.

• Another instrument will look at how your eyes move while you are reading. This fits on a headband around your forehead and shines an invisible light towards your eyes.

All of these tests are safe and have been used extensively in research. None of them are painful. The tests are not difficult to do although you may be asked to keep your eyes still.

If you were not taking part in the study, only refraction would normally be performed when you visit the hospital; all of the other tests would not be part of normal clinical care.

It is important that you are able to set aside enough time for each visit.

You will also still have to attend the medical retina clinic to see your eye doctor in the usual way. We will try and make the clinic and research visits on the same day when possible.

What do I have to do?

Apart from visiting the Institute for each appointment, there are no restrictions on your lifestyle. You can continue to take any medicines or eyedrops as normal.

What are the possible benefits of taking part?

Taking part in the study may help you to learn how to use “side vision” more effectively. However the results of the research are more likely to be of benefit to other people who develop macular disease in the future.

You will be given travel expenses and some money for lunch at the Friends’ cafeteria at each visit.

You can also have a low vision assessment (LVA) without having to go through the normal hospital waiting system.
I can review any glasses or magnifiers that you currently use and can supply any more appropriate devices, if possible.

**What happens when the research study stops?**

You will still be seen in the Medical Retina Clinic in the normal manner after the study stops.

**What if something goes wrong?**

The research does not carry any more risks than visiting the hospital in the normal way. If taking part in this research project harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms may be available to you.

**Will my taking part in this study be kept confidential?**

All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital or Institute will have your name and address removed so that you cannot be recognised from it.

Your general practitioner (GP) will be informed that you are taking part in this study, if you wish.

**What will happen to the results of the research study?**

The results will be published as part of a PhD thesis. They are also likely to be used at conferences or in papers (articles) in medical journals. You will not be identifiable from any published results of the study. If you wish, copies of research papers can be given to you.

**Who is organising and funding the research?**

The research is being carried out between Moorfields Eye Hospital and the Institute of Ophthalmology (part of University College London).
It is being supervised by Professor Gary Rubin of the Department of Visual Rehabilitation at the Institute. Professor Alan Bird and Dr Louise Culham at Moorfields are also involved in the study.

The study is being funded by the research fund of the Guide Dogs for the Blind Association (GDBA).

Who has reviewed the study?

The study has been approved by the Moorfields Research Ethics Committee.

Who can I contact for more information?

I am the person who will be carrying out most of the tests on you, and I can be contacted by telephone on 020-7608 6957 or by e-mail at m.crossland@ucl.ac.uk

My name is Michael Crossland and I am an optometrist working at both Moorfields and the Institute.

Thank you for taking the time to read this booklet.

Prepared by Michael Crossland
Version 2/November 2000
CONSENT FORM

The development of optimal viewing strategies in Macular disease

Principal Researcher: Michael Crossland BSc MCOptom

Please initial box

1. I confirm that I have read and understand the information sheet dated November 2000 (version 2) for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

3. I agree to take part in the above study.

Name of patient  Date  Signature

Name of Person taking consent  Date  Signature
(if different from researcher)

Michael Crossland  Date  Signature
Researcher
Appendix 3: Protocols for methods

To ensure that the methods used in this thesis are reproducible, this chapter will give protocols for each of the techniques described in chapter 2.

A3.1 Protocol for refraction

Patients were refracted in the vision rehabilitation research laboratory at the Institute of Ophthalmology, a room equipped with an ETDRS logMAR visual acuity chart positioned 4 metres from a comfortable patient chair.

Patients’ habitual distance spectacles were neutralised using a Topcon focimeter (LM-8, Topcon, Japan). A trial frame was placed on the patient, and spherocylindrical retinoscopy was performed on the study eye only, from a distance of 50 cm, whilst the other eye maintained distance fixation. The lens corresponding to the corrected retinoscopy result (i.e. without the +2.00 DS addition for the retinoscope distance) was inserted into the trial frame. The contralateral eye was then occluded. Subjective refraction was performed to refine the spherical component of the prescription, using spherical lenses of the smallest increment at which patients could appreciate a difference in vision, whilst patients observed a line of letters on the ETDRS chart. The cylindrical axis and power was checked using a negative cross-cylinder technique whilst patients observed a letter O on the ETDRS chart. Finally the spherical power was refined on the smallest observable line of letters. All lenses used were full aperture glass trial lenses, placed as close to the eye as was comfortable.

If the patient could not see any letters at the 4m viewing distance, the chart was repositioned to 2m for the purpose of refraction.

A3.2 Protocol for visual acuity measurement

Patients viewed the ETDRS chart from a distance of 4 metres with the refractive correction found above placed into the trial frame. The contralateral eye was occluded. Patients were asked to read the chart from the first letter onwards. When
patients claimed they were unable to read a letter, they were encouraged to guess. When patients read two or more letters on a line correctly, they were asked to read the next line. Scoring was achieved by recording the size of the last line of letters which was read correctly, with an addition of 0.02 log units for each letter on the chart read incorrectly.

A3.3 Protocol for contrast sensitivity measurement
Patients were asked to read the Pelli-Robson chart which was held at eye level one metre in front of the patient chair. Patients wore their optimal refractive correction in a trial frame with the contralateral eye occluded. Patients were asked to read from the top of the chart downwards. When patients claimed that they could not read a letter, they were encouraged to look at the letter for at least 20 seconds before making a guess. Testing finished when patients failed to identify any letters of a triad. Scoring was based on the last triad on which patients correctly identified any letters, with a 0.05 log unit reduction for every error made on the chart. For the purposes of scoring, O was classified as a correct response for the letter C, in the manner described by Elliott (1991).

A3.4 Protocol for microperimetry assessment
Patients were sat at the SLO with the chinrest adjusted to a comfortable height. The test eye was observed and the contralateral eye was occluded. The background screen luminance was set to 1 cd/m², the fixation cross height to 2.5° and the stimulus size to Goldmann III size. The fixation cross was displayed on the raster and moved around to ensure that the patient was able to see and follow the target. The cross was then set in the centre of the raster. An initial stimulus was presented at an area with presumed visual function. A distinctive retinal feature such as a vessel bifurcation or disc feature was used as the reference marker.

Further stimuli were presented in a roughly square array encompassing the fovea and ensuring that the edge of the scotoma was identified in each major meridian. Stimuli were presented in a pseudorandom order, determined by the investigator. Particular attention was made to visible areas of atrophy, hyper- or hypo-pigmentation and the border of the scotoma. If patients indicated that the task was becoming difficult they
were invited to sit back and take a rest before data collection recommenced. The same reference point was used throughout to ensure that an accurate map was created. When the investigator was satisfied that the microperimetry map accurately described the scotoma, a final retinal image was grabbed and the patient was invited to sit back from the SLO.

**A3.5 Protocol for gazetracker set-up and calibration**

Patients were asked to sit in a chair at 50cm from centre of the display monitor. Room lights were turned off, but the ETDRS chart was left on to provide background illumination for safety. The monitor height was adjusted to ensure that the centre of the screen was at the patient’s eye level. The non-examined eye was occluded with a simple eye patch, and an appropriate refractive correction (distance prescription +2.00DS) was placed into a trial frame using full aperture lenses. The eyetracker headset was placed on the patient’s head and the restraining straps were tightened until the patient reported that it felt firm yet comfortable. The camera was adjusted so that it gave a clear image of the eye, and the eye camera was adjusted to minimise the size of the corneal reflections from the focusing device. Pupil threshold was set automatically by using the Eyelink command “A.” The antireflection system was turned off.

Calibration was performed using the 5-point algorithm supplied with the eyetracker. Targets were enlarged to be 3 degree black circle with an 18’ central detail. Calibration was repeated, with careful instruction, until “good” calibration was reported by the eyetracker. Validation was then performed, followed by drift correction.
Appendix 4: Published papers

To date, three papers based on this thesis have been accepted for publication in peer-reviewed journals.

The first of these described the method of using the gazetracker for the measurement of fixation stability. This paper appeared in *Optometry and Vision Science* in 2002.

The second paper, describing the statistical techniques used, has been published in *Vision Research* in 2004.

The third paper is currently in press at *Ophthalmic and Physiological Optics*. A preprint copy of this paper can be found at the very end of this thesis.
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Evaluation of a new quantitative technique to assess the number and extent of preferred retinal loci in macular disease

M.D. Crossland a,*, M. Sims b, R.F. Galbraith b, G.S. Rubin a

a Division of Vision Rehabilitation Research, Institute of Ophthalmology, University College London, 11-43 Bath Street, London EC1V 9EL, UK
b Department of Statistical Sciences, University College London, Gower Street, London, WC1E 6BT UK

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Abstract

Patients with scotomas due to macular disease may use more than one preferred retinal locus (PRL) for fixation. We have developed and evaluated an objective, quantitative technique to determine the number of PRLs used during an episode of fixation and the extent of each locus. In five of eight adults with macular disease our techniques consistently indicated the presence of multiple PRLs. Patients with multiple PRLs were more likely to have suffered recent vision loss in the tested eye. Our technique describes fixation more fully than the traditional method of calculating a single bivariate contour ellipse area.

Keywords: Macular disease; Fixation; Retina; Human

1. Introduction

Patients with central vision loss due to macular disease are less able to hold steady fixation than those with good foveal function (Culham, Fitzke, Timberlake, & Marshall, 1993; Schuchard & Raasch, 1992; Steinman, Cushman, & Martins, 1982; White & Bedell, 1990; Whittaker, Budd, & Cummings, 1988). Assessment of fixation stability has been performed by many research groups interested in visual function in macular disease (Kosnik, Fikre, & Sekuler, 1986; Schuchard & Fletcher, 1994; White & Bedell, 1990; Whittaker et al., 1988).

Fixation stability has traditionally been quantified by calculating the area of an ellipse which encompasses fixation points for a given proportion (P) of eye positions during one fixation trial. This area is known as the Bivariate Contour Ellipse Area (BCEA) (Steinman, 1965). A smaller BCEA correlates to more stable fixation whereas if the eye “wanders” more then the BCEA will be larger. An example of a bivariate contour ellipse fitted to 10s of fixation data in a subject with normal vision fixating a circular target (as described in Section 2 below) is shown in Fig. 1. The BCEA is 553 minarc², consistent with data collected for subjects without disease in our laboratory (Crossland & Rubin, 2002).

Patients with central scotomas from macular disease use a preferred retinal locus (PRL) by viewing targets eccentrically rather than directly (Culham et al., 1993; Fletcher & Schuchard, 1997; Fletcher, Schuchard, & Watson, 1999; Schuchard, 1995; Schuchard & Fletcher, 1994; Schuchard, Naseer, & de Castro, 1999; von Noorden & Mackensen, 1962; White & Bedell, 1990; Whittaker, Cummings, & Swieson, 1991). Further, some authors have reported patients using two or more PRLs for fixation during one trial (Duret, Issenhuth, & Safran, 1999; Lei & Schuchard, 1997; Whittaker et al., 1988).

For the purpose of this study, our operational definition of a preferred retinal locus is “a circumscribed retinal area, used for fixation of a target for \( P \geq 10\% \) of the duration of a trial.”

If fixation is divided between multiple retinal areas then quantifying fixation stability using the BCEA technique can underestimate patients’ fixation ability. For example, if the patient exhibits good fixation in two closely circumscribed areas, calculation of a “global” BCEA would indicate very poor fixation whereas fixation may be relatively stable within the two locations.

Whittaker and co-workers defined subjects as displaying multiple fixation loci by assuming an arbitrary
maximum area for each PRL of 3° × 3° (Whittaker et al., 1988). This technique could overestimate fixation stability if the eye was drifting over a wider area without discrete loci being present. Other researchers have observed the retina during fixation but have only described multiple PRLs when very different areas of the retina were used for fixation (Duret et al., 1999; Lei & Schuchard, 1997).

In order to determine how many loci are present within one fixation trial, a test for multimodality is required. Formal statistical tests for detecting the number of multiple components exist (Titterington, Smith, & Makov, 1985), however they require the distance between the components to be large. An informal test such as the kernel density estimator (see Appendix A) can allow the number of components to be visually determined from a contour plot of the kernel density estimates.

We have developed a technique to calculate the number of PRLs during one set of fixation data and use an iterative process to determine the characteristics of each of these PRLs. We show that assigning a number of “local” BCEAs can describe data from these sorts of experiments more completely than one global BCEA can.

2. Method

2.1. Patients

Eight patients with macular disease and macular scotomas demonstrated on the Amsler test, were recruited from the Medical Retina and Low Vision clinics at Moorfields Eye Hospital in London. The Amsler test is not very sensitive to detecting the presence of macular scotomas (many false negatives, Schuchard, 1993) but it is reasonably specific (few false positives). Furthermore, the presence of a macular scotoma was subsequently verified with a scanning laser ophthalmoscope. Only those with non-treatable macular lesions, or those who had already had medical or surgical intervention, were included in the study. Exclusion criteria included diabetes mellitus, a history of psychiatric or neurological disease and ocular comorbidity other than visually insignificant cataract. The second eye to be affected was measured in recent onset cases. In long-standing macular disease the eye with the better acuity was used.

The study followed the Declaration of Helsinki and was approved by the Moorfields Eye Hospital ethics committee. Patients gave their informed consent prior to entering the study.

2.2. Assessment of fixation stability

Patients were asked to fixate a round, black target of 3° diameter with an 18° white central detail displayed against a white background on a computer monitor (Trinitron GDM-F500R, Sony, Japan). The background screen luminance was 125 cd/m², resolution was 800 × 600 pixels and the refresh frequency was 85 Hz. The target was displayed for a period of 10 s.

Eye position was measured with an SMI gazetracker (SensoMotoric Instruments, Germany) using Eyelink software (version 2.04). This eyetracker consists of two infra-red cameras which are mounted on a headband and record eye position using the “bright-pupil” technique. A further camera tracks head motion with respect to infra-red emitters mounted in front of the patient at the corners of the video display. Compensation for head motion is made so that a real position of gaze can be calculated. Eye position is measured at a temporal frequency of 250 Hz and the manufacturers report a gaze position accuracy of <0.5°.

Calibration, drift correction and validation were performed prior to stimulus display using the algorithms provided for this purpose. Only trials where the calibration was categorised as “good” by the Eyelink software were included. Calibration is described as “good” when minimal nonlinearity exists when fixating different target positions (maximum ratio of gains = 1.5:1 horizontally, 3:1 vertically (personal communication, SR Research, Osgoode, Canada)).

Although the eyetracker can measure both eyes independently and simultaneously, only data from the eye of interest was recorded. The contralateral eye was occluded.

Five practice trials were performed to ensure patient understanding of the task.

2.3. Data processing

The first second of data was discarded as it included eye movements whilst patients were finding the target on the screen. Although these data are of interest in terms
of the number of saccades and speed with which a patient can locate a newly presented stimulus, it was felt that they would detract from pure stability of fixation measurements. Similarly data recorded during saccades (where eye movement exceeds 30°/s) were excluded. Recordings taken 0.25 s before and 0.5 s after the start of a blink were removed to avoid the vertical artefact which is elicited by lid movement with our eyetracker. To ensure that we were not undersampling our data files excessively, the gazetracker was operated at the maximum temporal frequency (250 Hz) and only trials where more than 60% of data remained were used.

2.4. Statistical methods 1: calculation of a "global" BCEA

A “global” BCEA was calculated to encompass a given proportion of all fixation points, using the formula:

\[ \text{BCEA} = 2k\sigma_H\sigma_V(1 - \rho^2)^{1/2} \]

where \(k\) is the standard deviation of point location over the horizontal meridian, \(\sigma_V\) the standard deviation of point location over the vertical meridian, and \(\rho\) the product-moment correlation of these two position components.

The value \(k\) is dependent upon the probability area chosen (see Eq. (2))

\[ P = 1 - e^{-k} \]

where \(e\) is the base of the natural logarithm.

Therefore when \(k\) is 1, 63.2% of the fixation positions lie within this area.

Different authors have used different values of \(P\), such as 0.63 (Kosnik et al., 1986; Steinman, 1965), 0.68 (Culham et al., 1993; Nachmias, 1959) or 0.95 (Schuchard & Raasch, 1992).

For the purposes of this study, fixation data have been calculated with a \(P\) value of 0.68 \((k = 1.14)\) in order to remain consistent with previous research performed in this laboratory.

Fig. 2. (a) Cleaned data set, (b) global BCEA fitted to data \((\text{BCEA} = 21.725 \text{ minarc}^2)\), (c) contour plot produced by the KDE indicates three PRLs, (d) description of each locus returned by the EM algorithm and \(p\) = proportion of data points in each PRL.
2.5. Statistical methods 2: determining the number of PRLs present

The kernel density estimator (KDE) was applied to the reduced data set using software written in S-PLUS (v4.5, MathSoft Inc., Cambridge, MA) by MS. The window width was set at the optimum level described by Bowman and Foster (1992) and a contour plot of the density estimates was produced using a 50×50 grid. Appendix A gives a more complete description of the KDE. An example of an ambiguous data set which is processed by the KDE is shown in Fig. 2.

2.6. Statistical methods 3: determining the parameters of each PRL

After performing the KDE calculations, a mixture of component bivariate normal distributions was fitted to the data using the EM (expectation, maximisation) algorithm. The number of discrete peaks seen on the contour plot produced by the KDE was used as the number of components. The EM algorithm returns the estimated parameters of each bivariate normal distribution, the mean position and the standard deviation along the x and y axes, the correlation coefficient, a "local" BCEA for each locus (using Eq. (1)) and an estimate of the proportion of data which fell into each locus. The estimated parameters are those for which the log likelihood is highest. The algorithm calculates the value of the log likelihood and also the Bayesian information criterion (BIC) and the integrated classification likelihood (ICL-BIC) (McLaughlan & Peel, 2000). These can be useful to aid model selection (for example to determine the number of components if this is not clear from the KDE plot). The whole process was performed ten times using different starting values in order to check that the estimates converged to the correct final values.

Mathematical properties of the EM algorithm are discussed in Appendix B.

Linear regression and ANOVA analyses used elsewhere were performed using JMP software (version 4.0.4; SAS Institute, Cary, NC).

3. Results

3.1. Patients

One patient (aged 44 years) had Stargardt disease, a juvenile macular disease. The other seven suffered from age-related macular degeneration (mean age = 77.1 years, SD = 9.21). Four patients (50%) were male. Duration of disease varied from three weeks to many years.

The best visual acuity recorded was near normal (0.04 logMAR (20/22)) whilst the worst was 1.30 logMAR (20/400). There was no clear relationship between VA and either age or duration of disease.

3.2. Global BCEA

Global BCEAs calculated for all subjects varied from 1150 minarc² to 21100 minarc². No relationship was found between global BCEA and visual acuity ($r^2 = 0.19, p > 0.28$) or age ($r^2 = 0.04, p > 0.6$). However a highly significant difference was found in BCEA between those with recent vision loss (<4 months) and those with long standing macular disease ($t = 2.45, p < 0.001$; Fig. 3).

3.3. Number of PRLs

The KDE was applied to all data. In three cases (TB, AP, HP) the contour plot produced by the KDE program indicated one discrete locus of fixation. However in the remaining 5 patients, the KDE indicated the presence of two or three different fixation loci. Fig. 4 shows the kernel plots produced for each data set.

A local BCEA was calculated for each component. In each instance the sum of these local BCEAs was less than the global BCEA, being on average 58% of the size of the larger, global BCEA. Results from the EM algorithm for the 5 patients with multiple PRLs are shown in Table 2.

Visual acuity was moderately correlated with the number of PRLs ($r = 0.44$). The correlation between acuity and sum of the local BCEAs was somewhat stronger, however neither correlation was statistically significant ($p > 0.05$). Due to the small sample size, a randomization test was also used to test whether visual acuity was related to the number of PRLs or sum of local BCEAs. These correlations were not statistically significant (Number of PRLs, $p = 0.28$, 1000 randomizations; Sum of local BCEAs, $p = 0.10$, 1000 randomizations).

Fig. 3. The relationship between duration of disease and global BCEA. Diamonds represent 95% confidence intervals.
Fig. 4. Kernel plots for all of the subjects (except DP, whose plots can be found in Fig. 2).
Table 1
Full data for all eight patients

<table>
<thead>
<tr>
<th>Initials/age</th>
<th>Diagnosis</th>
<th>Time since vision loss</th>
<th>VA/logMAR</th>
<th>Global BCEA (minarc²)</th>
<th>n PRL</th>
<th>Σ local BCEAs (minarc²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS/60</td>
<td>AMD</td>
<td>3 weeks</td>
<td>0.74</td>
<td>15 900</td>
<td>2</td>
<td>7950</td>
</tr>
<tr>
<td>KB/76</td>
<td>AMD</td>
<td>&lt;4 weeks</td>
<td>0.22</td>
<td>21 110</td>
<td>2</td>
<td>2340</td>
</tr>
<tr>
<td>FG/90</td>
<td>AMD</td>
<td>&lt;4 weeks</td>
<td>0.56</td>
<td>14 500</td>
<td>3</td>
<td>9270</td>
</tr>
<tr>
<td>DP/76</td>
<td>AMD/MTS</td>
<td>12 weeks</td>
<td>1.30</td>
<td>21 700</td>
<td>3</td>
<td>9240</td>
</tr>
<tr>
<td>TB/80</td>
<td>AMD</td>
<td>&gt;2 years</td>
<td>0.62</td>
<td>1770</td>
<td>1</td>
<td>1770</td>
</tr>
<tr>
<td>AP/44</td>
<td>Stargardt</td>
<td>&gt;2 years</td>
<td>0.12</td>
<td>1150</td>
<td>1</td>
<td>1150</td>
</tr>
<tr>
<td>KD/75</td>
<td>AMD</td>
<td>&gt;2 years</td>
<td>0.04</td>
<td>7220</td>
<td>2</td>
<td>3260</td>
</tr>
<tr>
<td>HP/83</td>
<td>AMD</td>
<td>&gt;2 years</td>
<td>0.60</td>
<td>2160</td>
<td>1</td>
<td>2160</td>
</tr>
</tbody>
</table>

AMD = age-related macular degeneration, MTS = macular translocation surgery.

Table 2
Parameters of the PRLs for each patient with multiple PRLs

<table>
<thead>
<tr>
<th>Initials</th>
<th>PRL #</th>
<th>P</th>
<th>BCEA (minarc²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RS</td>
<td>1</td>
<td>0.78</td>
<td>5260</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.22</td>
<td>2690</td>
</tr>
<tr>
<td>KB</td>
<td>1</td>
<td>0.50</td>
<td>966</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.47</td>
<td>1370</td>
</tr>
<tr>
<td>FG</td>
<td>1</td>
<td>0.64</td>
<td>2220</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.20</td>
<td>3950</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.16</td>
<td>3100</td>
</tr>
<tr>
<td>DP</td>
<td>1</td>
<td>0.36</td>
<td>2400</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.31</td>
<td>2500</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.22</td>
<td>4340</td>
</tr>
<tr>
<td>KD</td>
<td>1</td>
<td>0.63</td>
<td>2250</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.37</td>
<td>1010</td>
</tr>
</tbody>
</table>

P = proportion of trial for which PRL is being used.

Table 3
Comparisons in the number of PRLs and the sum of local BCEAs found for two different trials and applications of the statistical procedure

<table>
<thead>
<tr>
<th>Subject</th>
<th>Number of PRLs</th>
<th>Σ local BCEAs (minarc²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trial 1</td>
<td>Trial 2</td>
</tr>
<tr>
<td>RS</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>KB</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>FG</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>TB</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>KD</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>HP</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

4. Discussion

We have applied novel statistical techniques to analyse fixation characteristics of subjects with macular disease.

Our results indicate that patients with newly presenting macular disease are more likely to display multiple PRLs, as defined by our statistical paradigm. Analysis of such patients’ fixation data using a global BCEA would be inappropriate as the statistical assumption of unimodality would no longer be valid.

It is perhaps surprising that some of our patients display two or even three loci over a relatively short fixation trial. Earlier control experiments did not find an increase in the number of PRLs or BCEA magnitude in longer fixation trials of 30 s (Bellmann, Feely, Crossland, Kabanarou, & Rubin, 2003).

Some patients (KB, DP) appear to split their fixation evenly across their multiple PRLs whereas others (RS, KD) rely on one location for the bulk of the trial. Other authors have found multiple PRLs only during a complex task such as reading (Duret et al., 1999) or when luminance is changed (Lei & Schuchard, 1997). It could be that our statistical technique is more sensitive in detecting multiple loci than the methods used by other groups. Our findings agree with those of Whittaker, who reports that 39% of patients exhibit multiple PRLs (Whittaker et al., 1988). Our technique is repeatable in finding the number of PRLs and the sum of the local BCEAs.
4.1. Equipment considerations

Infra-red eyetrackers have not been widely used in the assessment of fixation stability; in general the scanning laser ophthalmoscope (SLO) has been the instrument of choice. Although the SLO allows visualisation of the retina, stimuli are limited to monochromatic, monocular images presented at a fixed viewing distance. We have previously shown fixation stability measurements with these two instruments to be linearly related, with larger BCEAs being recorded by the eyetracker, which we believe to be due to its free-head nature (Crossland & Rubin, 2002). Van der Geest and co-workers found the same eyetracker to be comparable to a scleral search coil technique in the measurement of fixation position (van der Geest & Frens, 2002). The scleral coil technique was used by Whittaker in their study of multiple PRLs (Whittaker et al., 1988).

4.2. Limitations of the statistical technique

Because the EM algorithm is an iterative procedure, it is important to be aware of local maxima problems. These can cause the loci described by the EM algorithm to correspond poorly to the kernel plots. The statistical procedures we have used are quantitative, but not entirely automatic. When running the EM algorithm it was found to be important to compare the results it produced with the contour plot created by the KDE and to repeat the EM process with different starting values for the number of loci until the likelihood is maximised.

Calculation of a BCEA assumes that fixation points are normally distributed. Steinman (1965) found that small departures from normality occurred when examining the fixation behaviour of normally-sighted observers and concluded that “by and large, the area of a bivariate normal ellipse seems to be a good approximation when used to measure the variability of the fixating eye about its mean position.” It is generally accepted that the BCEA provides a useful summary of normal fixation data. However, multimodality is a more critical departure from the assumptions of a global BCEA than is non-normality. If the fixation data for patients are truly multimodal, as our analyses suggest, then the local BCEA will provide a better approximation than a global BCEA.

The selection of the window width is critical in determining the number of PRLs present. By changing the window width, data can be over- or under-smoothed. The window width which we use has been described as optimal for a range of distributions by Bowman and Foster (1992, 1993a, 1993b) and has been adopted by several computer based statistics packages, such as Matlab (MathWorks, Natick, MA). Fig. 5 compares a dataset which is smoothed by our optimal window width and by larger values. It can be seen that by manipulating the window width, more or fewer PRLs are determined. Further research is required to confirm the selection of window width which we are using is ideal. The window width has no effect on the EM algorithm. As different starting values were input into the EM algorithm and the most likely fit was taken, the final result will not be biased by the selection of window width.

Although we have shown that the position of gaze can fall within multiple loci in our patients, we do not
know that the patient can see the target at all times. Indeed it may be that when two gaze positions are found using this technique one corresponds to the non-seeing foveal centre and the other to a healthy retinal area.

It is also possible that our technique is finding individual clusters of localized drift areas within one large PRL rather than true multiple loci. However, as the separation between our PRLs is of the order of 20–40' (whereas typical drift amplitudes are around 2–5', Carpenter, 1988) and our technique is repeatable with regard to the number of clusters present, we believe that the KDE is determining truly different PRLs.

4.3. Duration of disease

Although we do not have enough data to state unequivocally that the number of PRLs diminishes with time, it appears that patients with long-standing macular disease display fewer PRLs than those with newly presenting disease. This is of great interest to those working in vision rehabilitation for patients with macular disease. It is tempting to hypothesise that, over time, patients will progress from having many PRLs to having just one, or that the multiple PRLs will coalesce into one larger locus of fixation.

If fixation characteristics do indeed change with time then this may explain the difficulty in correlating visual acuity with the properties of the PRL; if these patients were all at the same stage in their rehabilitation then perhaps a stronger correlation would exist. A prospective, longitudinal study is indicated to further investigate the development of fixation with time.

5. Conclusions

Our techniques introduce some objectivity into the assessment of fixation patterns and use less arbitrary guidelines for multimodality than previous techniques. In some circumstances it is not necessary to use such elaborate statistical tests as those described here, but in other cases it is difficult to group fixation points into neat clusters. For ambiguous data sets the quantitative technique we have described is useful to determine whether patients with macular disease use one or many PRLs. We have shown that our technique is repeatable within a subject.

With further development, we expect the kernel density estimator and expectation, maximisation algorithms to become of great benefit for researchers interested in visual behaviour in macular disease.

Acknowledgements

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Appendix A. The kernel density estimator

The use of a kernel density estimator in multivariate data is explained in detail elsewhere (Silverman, 1986). Briefly, if a sample of horizontal and vertical observations \( \left( x_1, y_1 \right), \ldots, \left( x_n, y_n \right) \) is collected with joint probability density function \( f(x, y) \) then the kernel density estimator for bivariate data is:

\[
\hat{f}(x,y) = \frac{1}{nh_xh_y} \sum_{i=1}^{n} K \left( \frac{x-x_i}{h_x}, \frac{y-y_i}{h_y} \right) \quad (i = 1, \ldots, n)
\]

where \( K(x,y) \) is the kernel function, such that:

\[
\int_{-\infty}^{\infty} K(x,y) \, dx \, dy = 1
\]

and \( h_x, h_y \) are window widths or smoothing parameters.

We used the following kernel function (Silverman, 1986):

\[
K(x,y) = \frac{1}{\pi} \exp \left( -\frac{1}{2} \left( x^2 + y^2 \right) \right)
\]

Bowman and Foster suggested the following optimal window widths (Bowman & Foster, 1992):

\[
h_x = \hat{\sigma}_x n^{-1/6}
\]

\[
h_y = \hat{\sigma}_y n^{-1/6}
\]

where \( n \) is the number of observations and \( \hat{\sigma}_x, \hat{\sigma}_y \) are estimated standard deviations of \( x \) and \( y \).

Appendix B. The EM algorithm

The EM algorithm is a method of calculating maximum likelihood estimates. Let \( y_i \) denote the \( (x,y) \) coordinates for the \( i \)th observation. The observed data \( y_1, \ldots, y_n \) can be regarded as incomplete since the components to which they belong are unknown. If \( z_{ij} = 1 \), \( y_i \) has a probability density function \( f_j(y; \mu_j, \Sigma_j) \), where \( f_j(y; \mu_j, \Sigma_j) \) is a bivariate normal density function with mean \( \mu_j(2 \times 1) \) and covariance matrix \( \Sigma_j(2 \times 2) \). Let \( z_i = (z_{i1}, z_{i2}, \ldots, z_{in})^T \) denote a multinomial vector indicating which component \( y_i \) is from. That is, exactly one of \( z_{i1}, \ldots, z_{in} \) equals 1 and the others equal 0. The probability that \( z_{ij} = 1 \) equals \( \pi_j \) (where \( \pi_1 + \pi_2 + \cdots + \pi_n = 1 \)) so \( \pi_j \) represents the proportion of time that the \( j \)th PRL is occupied. A complete data sample is therefore \( \left( z_{i1}, y_{i1} \right), \ldots, \left( z_{in}, y_{in} \right) \). It is assumed that all \( n \) observations are independent and have been fully categorised. The complete data log likelihood is:
\[ \ell_c(\theta) = \sum_{i=1}^{n} \sum_{j=1}^{k} z_{ij} \log \left( \pi_j f(y_i; \mu_j; \Sigma_j) \right) \]  

(B.1)

where \( \theta \) denotes the full set of parameters \( \pi_j, \mu_j, \Sigma_j \) for \( j = 1, 2, \ldots, k \).

The EM algorithm treats \( z_i, \ldots, z_n \) as missing data. It is an iterative procedure consisting of two steps, E (Expectation) and M (Maximisation).

### B.1. The E-step

The E-step calculates the expectation of the complete data log likelihood with respect to the missing data given the observed data \( y \) and current parameter values \( \theta \). The log likelihood is linear in the \( z_{ij} \) so the E step simply replaces \( z_{ij} \) by their expected values \( \pi_{ij} \) given \( y \) and \( \theta \). Thus:

\[ \pi_{ij} = E(z_{ij} | y; \theta) = \frac{\pi_j f(y_i; \mu_j; \Sigma_j)}{\sum_{l=1}^{k} \pi_l f(y_i; \mu_l; \Sigma_l)}, \]

\[ j = 1, \ldots, k, \quad i = 1, \ldots, n \]  

(B.2)

\( \pi_{ij} \) is the posterior probability that an individual with observed value \( y_i \) belongs to component \( j \) (for given \( \theta \)).

### B.2. The M-step

The M-step maximises \( \ell_c(\theta) \) with \( z_{ij} \) having been replaced by \( \pi_{ij} \). The parameters that maximise \( \ell_c(\theta) \) can be written down explicitly:

\[ \pi_j = \frac{1}{n} \sum_{i=1}^{n} \pi_{ij}, \quad j = 1, \ldots, k \]  

(B.3)

\[ \mu_j = \frac{1}{n \pi_j} \sum_{i=1}^{n} \pi_{ij} y_i, \quad j = 1, \ldots, k \]  

(B.4)

\[ \Sigma_j = \frac{1}{n \pi_j} \sum_{i=1}^{n} \pi_{ij} (y_i - \mu_j)(y_i - \mu_j)^T, \quad j = 1, \ldots, k \]  

(B.5)

These give updated estimates of the parameters \( \theta \) in the iterative procedure. Eq. (B.3) estimates the mixing proportion \( \pi_j \), as the average of the posterior probabilities \( \pi_{ij} \) of all \( n \) observations for component \( j \). Eqs. (B.4) and (B.5) calculate the weighted average of the \( n \) observations and the weighted sample covariance matrix respectively, both using weights of \( \pi_{ij} \).

Before applying the EM algorithm, initial values for the parameters \( \theta^{(0)} \) are assigned. The E and M steps are then repeated until some stopping criterion is met. The stopping criterion is based on the relative change in the log likelihood \( \ell(\theta^{(k+1)}) - \ell(\theta^{(k)}) \) and (BCEA) \( ^{k+1} \) - (BCEA) \( ^{k} \) at each iteration \( (k = 1, 2, 3, \ldots) \). The program stops when the log likelihood is less than \( 10^{-4} \) and the BCEA is less than \( 10^{-3} \). The maximum number of iterations is set at 200. Throughout the E, M process \( L(\theta^{(k+1)}) \geq L(\theta^{(k)}) \), where \( \theta^{(k)} \) are the parameter values after \( k \) iterations.

### References


Fixation stability and reading speed in patients with newly developed macular disease*

Michael D. Crossland, Louise E. Culham and Gary S. Rubin

Division of Vision Rehabilitation Research, Institute of Ophthalmology, University College London, 11-43 Bath Street, London ECIV 9EL, and Department of Optometry, Moorfields Eye Hospital NHS Trust, London, UK

Abstract

Background: Patients with macular disease and central scotomas must use a peripheral, preferred retinal locus (PRL) in place of their damaged fovea. This paper investigates the development of the PRL, with particular reference to the stability of fixation.

Methods: Twenty-five patients with age-related and juvenile macular disease were recruited. All patients had developed a scotoma in their better eye within the previous 2 weeks. Patients were assessed using a scanning laser ophthalmoscope and an infra-red gazetracker on four further occasions over the next 12 months.

Results: A linear relationship exists between reading speed and fixation stability for patients and control subjects. Fixation stability was not related to scotoma size, visual acuity or contrast sensitivity. Changes in fixation stability account for 54% of the variance in change in reading speed over the course of this study.

Conclusions: The deficit in reading speed in patients with macular disease can be partially attributed to impairments in fixation stability.

Keywords: low vision, macular disease, preferred retinal locus, reading

Introduction

The World Health Organisation estimates that 8 million people are severely visually impaired because of age-related macular disease (AMD) (World Health Organisation, 1997). AMD is the most common cause of blindness in the developed world and is the primary diagnosis of half of all patients registered as blind in the UK (Vingerling et al., 1995; Evans et al., 1996). The incidence of AMD appears to be increasing more rapidly than can be accounted for by the ageing of the population (Evans and Wormald, 1996). Juvenile macular diseases such as Stargardt’s and Best’s disease are less prevalent but are still a major cause of partial sight registration in the UK working age population (Evans et al., 1996).

Patients with bilateral scotomas due to macular disease must use peripheral retina in place of the damaged fovea. Many patients exhibit one discrete ‘preferred’ retinal locus (PRL) at a para- or extra-foveal location which they use for visual tasks (Timberlake et al., 1986; White and Bedell, 1990; Schuchard and Raasch, 1992; Guez et al., 1993).

Fixation stability

When the eye fixates upon a point, there is some retinal motion due to involuntary eye movements such as physiological nystagmus, drifts and microsaccades as well as correcting movements to compensate for motion of the head (Steinman et al., 1982; Carpenter, 1988). In
those without eye disease, the locus of fixation will lie within the foveola. In patients with bilateral scotomas, fixation will lie within the PRL.

A bivariate contour ellipse has been shown to describe the locus of fixation in normal observers (Steinman, 1965). The area of this ellipse [bivariate contour ellipse area (BCEA)] gives an indication of fixation stability, with larger areas corresponding to poorer fixation stability. The BCEA of individuals without macular disease is around 80–1200 minarc² (Steinman, 1965; Kosnik et al., 1986; Timberlake et al., 1986; Culham et al., 1993; Rohrschneider et al., 1995; Crossland and Rubin, 2002). With macular disease, they range from near-normal values to over 13 000 minarc² (Culham et al., 1993; Schuchard and Fletcher, 1994; Rohrschneider et al., 1995).

Fletcher and colleagues devised a ‘PRL scoring’ system based on fixation stability, pursuit ability and ‘saccade to PRL’ ability (Fletcher et al., 1993; Schuchard and Fletcher, 1994). They found that this score was superior to visual acuity in predicting reading speed and accuracy in patients with central scotomas. Rohrschneider et al. (1995) found that ‘functional impairment’ was associated with decreased fixation stability. Rohrschneider's group determined fixation stability as being poor only when the standard deviation from the mean fixation point was > 3°, which is roughly equivalent to a BCEA of 100 000 minarc². This indicates exceptionally poor fixation stability.

Multiple PRLs

Initially it was assumed that most patients develop one, well-defined PRL (Cummings et al., 1985; Timberlake et al., 1986, 1987). However, more recent work has suggested that patients may use multiple PRLs during one task (Guez et al., 1993; Lei and Schuchard, 1997; Duret et al., 1999). It has been suggested that patients with scotomas larger than 20° are more likely to develop several PRLs than those with smaller lesions (Whittaker et al., 1988).

There are marked methodological problems with assessing whether patients display multiple PRLs. Although in some circumstances it is obvious that a patient has multiple PRLs (for instance when one horizontally shifted and one vertically shifted PRL is used), at other times it is difficult to determine whether a patient truly has multiple loci or whether fixation remains within one, poorly defined PRL. In collaboration with statisticians at University College London, we have developed a test for multimodality which can identify the number of PRLs present during a fixation trial and the fixation stability within each of these loci (Crossland et al., 2004).

The development of the preferred retinal locus (or loci)

Based on a cross-sectional study of patients with macular disease, White and Bedell suggested that ‘patients with longer duration since onset of [macular disease] showed oculomotor behaviours qualitatively more like those of normals’ (White and Bedell, 1990).

In order to fully assess the development of viewing strategies in macular disease, a longitudinal study design is required. The study described in this paper is the first such analysis of visual behaviour in macular disease. This paper reports the development of the PRL and fixation stability in a cohort of subjects for up to 12 months following the development of a scotoma in the second eye to be affected by macular disease.

Methods

Patients

Twenty patients with age-related macular disease (AMD) and five with juvenile macular disease (JMD) were recruited from the medical retina and low vision clinics at Moorfields Eye Hospital. All patients had developed symptoms in the previous 2 weeks in their second affected eye and had a central scotoma observable on scanning laser ophthalmoscopy. Patients had a primary diagnosis of AMD, Stargardt's disease or Best's disease and had no ocular comorbidity other than visually insignificant cataract. Eight control subjects were recruited, in two groups: five were age matched to the AMD patients and three to the JMD group. Control subjects had normal or corrected to normal vision and no evidence of ophthalmological disease on fundoscopy (and other tests as indicated).

All patients and subjects spoke English as their first language and none had any neurological impairment. Participants gave their informed consent and the study conformed to the tenets of the Declaration of Helsinki. The study was approved by the Moorfields Eye Hospital ethics committee.

Visit schedule

Patients were assessed within 2 weeks of recruitment (that is, within 1 month of the onset of symptoms). Subsequent visits took place 1, 3, 6 and 12 months after the baseline assessment. Patients still attended their normal medical retina outpatient clinic appointments. Appropriate low vision aids (LVAs) were prescribed for all patients by the investigator at the baseline assessment.
Fixation stability in macular disease: M. D. Crossland et al.

Fixation stability took place at any visit at which the patient reported difficulties with their devices. No training was provided, other than general instruction in the use of prescribed devices. Control subjects attended twice: at recruitment and after 12 months.

Patients whose macular disease worsened over the course of the study were removed before the planned end-date and only data from before the deterioration were analysed. Deterioration was defined as an increase in scotoma area of 0.5 disc areas or more, or a 0.2 logMAR (10 letter) drop in distance visual acuity.

Investigation

All investigation was performed on the better eye only, as fixation behaviour under binocular conditions is thought to be determined by the better eye rather than the patient's dominant or preferred eye (Schuchard et al., 1995; Kabanarou et al., 2003). The contralateral eye was occluded using a simple eye-patch.

At each visit, patients were refracted and their visual acuity and contrast sensitivity were measured with ETDRS and Pelli-Robson charts, respectively (Bailey and Lovie, 1976; Pelli et al., 1988).

Scotoma size

The size of the absolute scotoma was measured using a Scanning Laser Ophthalmoscope (SLO) (SLO-101; Rodenstock, Dusseldorf, Germany) running a microperimetry module (Scotometry v.3.1b; Rodenstock). A full description of microperimetry can be found elsewhere (Sunness et al., 1995; Varano and Scassa, 1998). Briefly, the patient is asked to fixate a central cross whilst reporting, by means of a button press, when they see a point target which is presented at a retinal location selected by the investigator. The stimuli used were Goldmann III size targets of intensity 200 cd m⁻² and were presented for 200 ms. In between presentations the investigator marked a distinctive retinal feature (for example a vessel bifurcation). Superimposition of these images creates a map of seeing and non-seeing retina. The size of the dense scotoma was recorded in disc areas.

Fixation stability

Fixation stability was recorded whilst patients fixated a target in each of five positions of gaze (directly ahead, 18° to the left and the right of the central position and 12° above and below the centre). The stimulus was a round, black target of 3° diameter with an 18° white central detail displayed against a white background on a computer monitor (Trinitron GDM-F500R; Sony, Tokyo, Japan). The background screen luminance was 125 cd m⁻², resolution was 800 × 600 pixels and the refresh frequency was 85 Hz. The target was displayed for a period of 10 s in each of the five locations, in a randomised order. Patients viewed the screen from a distance of 50 cm and wore an appropriate refractive correction of + 2.00 DS over their distance prescription.

Patients were instructed to look at the centre of the target and to keep their eyes as steady as possible.

Eye position was measured during the fixation trials with a SMI gazetracker (SensoMotoric Instruments, Berlin, Germany) using Eyelink software (version 2.04). This eyetracker consists of two infra-red cameras which are mounted on a headband and record eye position using the 'bright-pupil' technique. A further camera tracks head motion with respect to infra-red emitters mounted in front of the patient at the corners of the video display. Compensation for head motion is made so that a real position of gaze can be calculated. Eye position is measured at a temporal frequency of 250 Hz and the manufacturers report a gaze position accuracy of <0.5°. Independent comparison of this gazetracker with a scleral coil eyetracker has found agreement to within 1° between gaze positions recorded with these two systems (van der Geest and Frens, 2002).

Calibration, drift correction and validation were performed prior to stimulus display using the algorithms provided for this purpose. Only trials where the calibration was categorised as 'good' by the Eyelink software were included. Calibration is described as 'good' when minimal non-linearity exists when fixating different target positions [maximum ratio of gains = 1.5:1 horizontally, 3:1 vertically (personal communication, SR Research Ltd, Osgoode, Canada)].

Data were retrospectively analysed using a Matlab program written specifically for this purpose. Data analysis consisted of four stages. First, the first second of data was removed to allow patients to find the target on the screen. Second, data recorded immediately preceding and following any blinks were removed. Next, eye positions recorded during a saccade (velocity > 30° s⁻¹) were removed. Finally, a bivariate contour ellipse was calculated using the following equation (Steinman, 1965):

\[ \text{BCEA} = 2k \pi \sigma_H \sigma_V (1 - \rho^2)^{1/2} \]

where \( \sigma_H \) is the standard deviation of point location over the horizontal meridian, \( \sigma_V \) the standard deviation of point location over the vertical meridian, \( \rho \) the product-moment correlation of these two position components and \( k \) is defined by:

\[ P = 1 - e^{-k} \]

where \( P \) is the proportion of points which lie within the ellipse and \( e \) is the base of the natural logarithm. For the
purposes of this study, fixation stability was calculated with $P = 0.68$ ($k = 1.14$) to remain consistent with previous research performed in this laboratory.

The BCEA was converted from pixels$^2$ to minarc$^2$ using a simple transformation. Mean BCEA for the five positions of gaze was recorded.

**Multiple PRLs**

The presence of multiple PRLs was assessed using the kernel density estimator (KDE). The KDE was applied using software written in S-PLUS (v4.5, MathSoft Inc., Cambridge, MA, USA). The window width was set at the optimum level described by Bowman and Foster (1992) and a contour plot of the density estimates was produced using a 50 × 50 grid.

Where multiple PRLs were identified, a mixture of component bivariate normal distributions was fitted to the data using the expectation, maximisation (EM) algorithm. The number of discrete peaks seen on the contour plot produced by the KDE was used as the number of components. The EM algorithm calculates a 'local' BCEA for each locus (using equation 1) and an estimate of the proportion of data which fell into each locus. A more thorough description of these statistical techniques can be found elsewhere (Crossland et al., 2004). Where multiple PRLs were identified, the sum of the local BCEAs was used for analysis.

**Reading speed**

Reading speed was recorded using text presented at three times threshold visual acuity size on a computer monitor set 50 cm in front of the patient. This print size was selected since the minimum acuity reserve reported for 'high fluency' reading in macular disease patients is 3:1 (Whittaker and Lovie-Kitchin, 1991; Lovie-Kitchin et al., 2000; Massof, 2003). Ten sentences were randomly selected from a database of over 500 sentences and had similar properties to those used on the MNRead card (Legge et al., 1989) in terms of difficulty, length and word order. The sentences had a Flesch–Kincaid Grade level of 4.6. Sentences were displayed in Times New Roman font over two lines, without splitting words, in the centre of the screen. The left hand side of each line was justified. Participants were asked to read each sentence out loud as quickly as they could without making errors. Timing commenced at the moment the sentence appeared. A keystroke made by the investigator when the last word was read correctly stopped a timer in the computer. The mean time taken to read a sentence was recorded. If the sentence was read incorrectly then it was excluded from the analysis, unless the patient corrected their error.

**Results**

**Length of follow-up**

Eighteen patients completed 12 months of follow-up and seven were removed earlier due to their scotoma size increasing: six after 6 months and one after 3 months. All control subjects were assessed at baseline and after 1 year.

**Fixation stability**

As BCEA values for patients were not normally distributed (Shapiro–Wilk test, $W = 0.85$, $p > 0.5$), a natural log transform was performed to normalise them ($W = 0.98$, $p < 0.01$).

The mean BCEA for control subjects was 1614 minarc$^2$ at baseline (S.D. = 1022) and 1270 minarc$^2$ (S.D. = 574) at 12 months. There was no statistical difference between these values (repeated measures ANOVA, $p = 0.40$).

For patients, mean InBCEA at baseline was 9.04 log units (S.D. = 1.16), and 9.00 log units at the exit from the study (S.D. = 1.44). These log values correspond to 8440 and 8100 minarc$^2$, respectively. These values are far poorer than those for control subjects (Student’s $t$-test, $p < 0.001$ at entrance and exit).

In patients, the size of the BCEA was not associated with visual acuity (at baseline, $r = 0.38$, $p = 0.1$; at exit, $r = 0.36$, $p = 0.1$), contrast sensitivity (baseline $r = -0.09$, $p = 0.62$; exit $r = -0.10$, $p = 0.74$) or scotoma size (baseline $r = 0.13$, $p = 0.54$; exit $r = 0.20$, $p = 0.38$).

**The number of PRLs**

At the baseline assessment, 16 patients (64%) displayed multiple PRLs for targets presented in at least one of the five locations. Within these 16 patients, the mean number of PRLs used for the five screen positions was 1.7 (range 1.2–3.8). Although patients with multiple PRLs tend to have poorer fixation stability than those who use only one locus of fixation this result does not reach significance ($p = 0.08$). By the exit point of the study, 11 patients (44%) displayed multiple PRLs.

**Reading speed**

At baseline, mean reading speed for patients was 85 words min$^{-1}$ (S.D. = 37). By the exit point of the study, mean reading speed had fallen to 73 words min$^{-1}$ (S.D. = 38). Control subjects' reading speed remained

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**Figure 1.** The relationship between fixation stability and reading speed at the baseline assessment for patients (filled triangles, solid line) and control subjects (open squares, broken line). Line shows linear regression; patients: $r^2 = 0.21$; controls: $r^2 = 0.44$.

constant throughout the study (mean ± S.D. reading speed at baseline 187 ± 28 words min$^{-1}$; at 12 months 192 ± 22 words min$^{-1}$; $p = 0.68$).

**Fixation stability and reading speed**

For control subjects, a negative correlation was found between BCEA and reading speed at baseline assessment ($r = -0.66$, $p < 0.05$). This indicates that control subjects with poorer fixation stability read more slowly than those with smaller BCEAs. A similar relationship was found in patients at the baseline assessment (linear regression, $r = -0.45$, $p < 0.05$) and at the exit point ($r = -0.51$, $p < 0.05$). Figure 1 shows the relationship between fixation stability and reading speed for patients and control subjects at their baseline assessment.

Improvement in fixation stability was defined by subtracting $\ln(\text{BCEA}_{\text{exit}})$ from $\ln(\text{BCEA}_{\text{baseline}})$ (i.e. calculating the ratio of fixation stability at exit to that at baseline, with positive values corresponding to an improvement in fixation stability). The improvement in fixation stability accounts for 54% of the variance in reading speed (linear regression, see Figure 2).

**Discussion**

Fixation stability is significantly impaired in patients with macular disease. This reinforces the findings of previous research (Culham et al., 1993; Schuchard and Fletcher, 1994; Rohrschneider et al., 1995). The level of this impairment in stability does not appear to be associated with clinical features such as visual acuity, contrast sensitivity or scotoma size in our patients.

It is perhaps surprising that there is no relationship between scotoma size and fixation stability, as fixation is known to be less precise as eccentricity increases (Sansbury et al., 1973), and a larger scotoma will lead to a more eccentric PRL being used. However, this lack of correlation has been reported previously (Timberlake et al., 1986; White and Bedell, 1990).

It is important to note that only the size of the dense scotoma has been measured, and that the size of any area of relative scotoma is unknown. The apparently idiosyncratic nature of the variation in fixation stability may be attributable to the extent of the relative scotoma.

In subjects without macular disease, fixation stability appears to be related to suprathreshold reading speed. Although the limited number of control subjects assessed in this study preclude detailed analysis of these data, our results corroborate those for patients with reduced reading speed due to dyslexia, which suggest that fixation stability is a corollary of reading speed (see e.g. Eden et al. 1994).

In the presence of macular disease there is a weaker relationship between reading ability and fixation stability, with around 20% of the variance in reading speed being accounted for by fixation stability. Although there is no systematic change in fixation stability in patients, those small changes that do occur are related to changes in reading speed.

The BCEA values reported in the present study are larger than those found by researchers who have measured fixation stability using a SLO (Culham et al., 1993; Schuchard and Fletcher, 1994; Rohrschneider et al., 1995). We have previously shown that fixation stability measurements made with the infrared eyetracker are...
about 2.2 times larger than those made with the SLO and that there is a linear relationship between values obtained with these two instruments in control subjects (Crossland and Rubin, 2002) and in patients with central macular disease (Crossland et al., 2002). This difference in the size of the BCEA has been attributed to the free-head nature of the eyetracker; small eye movements are made to compensate for head motion when the head is unsupported (Steinman et al., 1982; Carpenter, 1988; Crossland and Rubin, 2002).

Unfortunately, far fewer patients with juvenile macular diseases were recruited than with AMD. Informal analysis of our data does not indicate any difference in fixation stability or reading speed between these two groups, although the low number of JMD patients recruited precludes any between groups analysis of these types of macular disease. JMD recruitment was limited by the far rarer incidence of these diseases and the different mode of onset of juvenile macular diseases.

This study is the first to have used the technique of calculating local BCEAs in the case of multiple PRLs. We have previously shown this technique to be repeatable in determining both the number of PRLs present and the sum of the local BCEAs (Crossland et al., 2004).

These results have implications for the design and practice of training exercises used in the rehabilitation of patients with macular disease. Several research groups advocate the use of visual training in macular disease (Goodrich and Mehr, 1986; Nilsson et al., 1998, 2003). In some cases, reading speed improves dramatically with training; the most recent paper by Nilsson and colleagues reports an average increase in reading speed from 9 to 68 words min⁻¹ (Nilsson et al., 2003). Although these investigators have not formally measured fixation stability in the manner performed in the present study, our results of this study suggest that an improvement in fixation stability may be at least partly responsible for the reported improvement in reading speed.

As changes in fixation stability only account for about half of the change in reading speed, other adaptive strategies are also likely to play a role in determining patients’ rehabilitation. These strategies are likely to include eye movement characteristics such as the number of saccades used to find the PRL and the nature of these saccades (White and Bedell, 1990; Whittaker and Cummings, 1996; McMahon et al., 1991, 1993; Whittaker et al., 1991; Fletcher et al., 1993).

Conclusion

Reading speed in control subjects and in patients with macular disease is associated with fixation stability. In patients, changes in fixation stability over the first 12 months after losing central vision account for 52% of the variance in reading speed change over the same period. These findings have implications for the design and implementation of training programs for patients with central field loss and for clinicians involved in the counselling of patients with this debilitating disease.

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