REFRACTIVE SURGERY FOR IATROGENIC AND CONGENITAL ANISOMETROPIA AND MILD VISUAL IMPAIRMENT

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Academic Dissertation
To be publicly discussed, with the permission of the Medical Faculty of the University of Helsinki, in the Seth Wichmann Auditorium of the Department of Obstetrics and Gynecology, Helsinki University Central Hospital, Haartmaninkatu 2, Helsinki, on November 26th, 2010, at 12 noon.

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Yliopistopaino
Helsinki 2010
To Arto and Aaro
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1 LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications, which are referred to in the text by Roman numerals I – IV:


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# 2 Abbreviations

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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>BOLD</strong></td>
<td>Blood-oxygenation-level-dependent</td>
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<tr>
<td><strong>BSCVA</strong></td>
<td>Best (spectacle) corrected visual acuity</td>
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<td><strong>D</strong></td>
<td>Diopter</td>
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<td><strong>fMRI</strong></td>
<td>Functional magnetic resonance imaging</td>
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<td><strong>LASEK</strong></td>
<td>Excimer Laser Epithelial Keratomileusis</td>
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<td><strong>LASIK</strong></td>
<td>Laser Assisted Sub-Epithelial Keratomileusis</td>
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<td><strong>mffMRI</strong></td>
<td>Multifocal functional magnetic resonance imaging</td>
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<tr>
<td><strong>PRK</strong></td>
<td>Photorefractive keratectomy</td>
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<td><strong>RPE</strong></td>
<td>Retinal pigment epithelium</td>
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<td><strong>RRD</strong></td>
<td>Rhegmatogenous retinal detachment</td>
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<td><strong>RS</strong></td>
<td>Refractive surgery</td>
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<tr>
<td><strong>SE</strong></td>
<td>Spherical equivalent</td>
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<tr>
<td><strong>UCVA</strong></td>
<td>Uncorrected visual acuity</td>
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<tr>
<td><strong>V1</strong></td>
<td>Primary visual cortex</td>
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3 Abstract

Background

During the last three decades, excimer laser refractive surgery (RS) has been increasingly used for the correction of refractive errors. Extensive literature has been published on the effect of myopic refractive surgery on visual acuity. Yet only few studies concerning the use of laser refractive surgery in adult anisometric and visually impaired patients are to be found in the literature. In anisometropia, the patient’s two eyes have unequal refractive power. To date there has been no wide interest in investigating the treatment of visual deficiencies in adult patients because visual deficiencies are thought to be irreversible after the first decade of life. There is, however, accumulating evidence that neural plasticity also exists in adult brains.

Objective

The aim of this study was to investigate functional outcome of excimer laser refractive surgery in adult anisometric and visually impaired patients. An additional goal was to examine changes in the primary visual cortex (V1) using multifocal functional magnetic resonance imaging (mffMRI) after laser refractive surgery for anisometropia and myopia.

Materials and Methods

Study I comprised 57 patients presenting with myopic anisometropia of ≥3.25 diopters (D). One hundred and seventy-four isometric myopic controls formed the control group. PRK or LASIK was performed on both anisometropic patients and myopic control subjects. As 43 of the myopic control subjects had bilateral surgery, altogether 217 myopic control eyes were included. BSCVA, refraction and refractive correction were measured preoperatively and 1, 3, 5-7, 8-13 and 25 months postoperatively. In Study II ten patients with a history of one or more RRD surgeries and following refractive surgery were enrolled. Eight out of ten patients had anisometropia of ≥ 2.5 D before refractive surgery. Patients were followed up for over 40 months after refractive surgery and invited for ophthalmological
examination to evaluate the long-term effectiveness and safety of excimer laser treatment in this patient population.

In Study III we evaluated the visual and refractive outcome of refractive surgery on mildly visually impaired adult patients (preoperative BSCVA on a log-MAR scale ≤-0.1, on Snellen scale ≤0.8). Two analyses were made of this study population. Cohort one was composed of eleven patients and nine non-amblyopic control subjects who had been treated with PRK and who had had control visits at 5-7, 8-13 and 14-24 months postoperatively. Cohort two comprised 41 visually impaired patients and 54 controls who had attended postoperative control at 14-24 months postoperatively.

Study IV was a prospective follow-up trial examining the changes in the primary visual cortex after refractive surgery. Two anisometropic patients and two isometropic myopic patients were examined with a 61-region mffMRI before RS and at three, six, nine and twelve months postoperatively. Two control subjects without refractive surgery were also examined with mffMRI at the beginning and at the end of the study.

Results

In Study I a significant improvement in BSCVA among myopic control subjects was evident 3 months postoperatively. The improvement in BSCVA was significantly slower for anisometropic patients. The improvement became statistically significant only 8-13 months postoperatively in anisometropic patients and appeared to persist to the end of the follow-up (24 months).

As expected, the mean degree of anisometropia increased after RRD surgery [mean 4.2±2.8D (range 0.00 to 8.25)] in Study II. At the ophthalmological re-examination 67±14 months after RS, mean anisometropia had decreased to 1.2±0.7D (range 0.00 to 2.75 D). The BSCVA either improved or remained the same in eight out of ten RRD patients after RS. When visual performance before RRD surgery was compared to the visual performance after RS, a statistically significant improvement in BSCVA was found.

In Study III there was a statistically significant improvement in BSCVA among visually impaired patients both in cohorts one and two. The difference in mean BSCVA between visually impaired patients and control subjects diminished during follow-up. Statistically tested, in cohort one, the BSCVA of the controls was found to be significantly better only preoperatively.

Both anisometropic patients attending fMRI study improved their BSCVA after RS. No visible differences in the stimulus evoked BOLD fMRI responses could be found between anisometropic patients, isometropic myopic patients and control subjects either pre- or postoperatively. Nevertheless a dramatic decrease in the num-
ber of active voxels in the fovea was found among anisometropic patients. Twelve months postoperatively the number of activated voxels in fovea had diminished by 65% compared to the preoperative situation in the operated anisometropic eyes. In unoperated anisometropic eyes the corresponding value was 86%. In myopic patients and control subjects the decreases in the number of active voxels were 31 % and 1 % respectively.

**Conclusion**

The results presented in this dissertation revealed that refractive surgery may be used successfully for the treatment of anisometropic adults with both congenital and iatrogenic anisometropia and for mildly visually impaired adults. The slower improvement in BSCVA for anisometropic patients compared to control myopic subjects suggested plastic changes in the visual cortex after refractive surgery. The mean improvement of nearly two Snellen lines 14-24 months postoperatively in visually impaired adults suggested plasticity of the visual system well beyond the conventional “critical period”. Our finding demonstrating a dramatic decrease in the number of activated voxels in the fovea of anisometropic patients after RS supports our hypothesis of plastic changes in the visual cortex of adult patients after RS.
Excimer laser refractive surgery has been widely used for the correction of refractive errors since its introduction in the 1980s. It has been postulated that to date several million surgical procedures with PRK and LASIK have been performed to treat ametropia. Despite the increasing number of these corrections, only little is known about refractive surgery on adult anisometropic and visually impaired patients.

In anisometropia, the refractive power of the eyes is unequal. Anisometropia may be congenital or iatrogenic. RRD surgery can, for example, cause anisometropia by affecting the axial length of the eye [Burton et al. 1977, Malukiewicz-Wisniewska and Stafiej 1999, Smiddy et al. 1989]. Anisometropia may be associated with impaired stereoacuity or binocular function [Brooks et al. 1996, Oguz and Oguz 2000, Simpson 1991]. It is generally accepted that a difference in refractive power exceeding 3 D will cause fusion problems and lead to suppression of the non-dominant eye [Milder and Rubin 2004], which especially in a developing eye of a child may lead to amblyopia. Patients with anisometropic amblyopia have significant interocular differences in their contour detection thresholds [Chandna et al. 2001] suggesting that the processing of ocular input to the visual cortex is impaired.

Visual deficiencies are thought to be irreversible after the first decade of life and therefore little effort has been made to treat adults’ visual deficiencies. However, accumulating evidence suggests that neural plasticity exists also in the adult visual system [Chino et al. 1992, Gilbert and Wiesel 1992, Henriksson et al. 2007, Levi and Polat 1996, Raninen et al. 2007]. On the basis of earlier studies, we hypothesized that adult patients’ visual impairment might be reversed by refractive surgery. This would have a huge impact on patients’ visual capacity and quality of life.

The aim of the present study was thus to investigate the functional outcome of excimer laser refractive surgery on adult anisometropic and visually impaired patients. We also examined the changes in the primary visual cortex which the refractive surgery may cause in adult anisometropic and myopic patients.
5 REVIEW OF THE LITERATURE

5.1 ANATOMY OF THE EYE

Light waves pass through the transparent cornea and lens before they reach the light sensitive neurons of the retina (Figure 1). Having a refractive power of 43 D (two thirds of the refractive power of the eye), the cornea is the most important refractive structure in the eye. Only very modest changes in the surface of the cornea can greatly affect the refractive power and the performance of the eye. The cornea is avascular and has an average thickness of 520 μm at its center [Lang 2007]. It consists of five distinct layers; epithelium, Bowman’s layer, stroma, Descement’s membrane and endothelium (Figure 2). The epithelium consists of stratified nonkeratinized squamous cells. The epithelium regenerates constantly thus wounds in the epithelium heal quickly. Contrary to the epithelium, Bowman’s layer does not regenerate. If injured, it is replaced by scar tissue. The stroma is the thickest part of the cornea, accounting for 90% of its thickness. Descement’s membrane, which serves as a basement membrane for the endothe-
lium, thickens with age [Johnson et al. 1982]. The endothelium, lying between Descemet’s membrane and the anterior chamber, plays a crucial role in healthy cornea. The endothelium sustains the clarity of the cornea and prevents the cornea from swelling by actively pumping the water from the stroma to the anterior chamber.

Figure 2. Layers of mouse cornea. Please note that mouse’s cornea lacks Bowman’s membrane. Courtesy: Niko Setälä

The cornea is an extremely sensitive organ; there is a great number of sensory nerve fibers and autonomic nerve fibers are also present [Muller et al. 2003]. There has been increasing interest in the study of corneal innervation as the use of refractive surgery has become popular [Avunduk et al. 2004, Linna et al. 2000, Moilanen et al. 2003, Moilanen et al. 2008, Patel and McGhee 2009]. Corneal innervation plays a key role in the healthy cornea; neuronal injuries significantly impair the ability of the cornea to heal itself [Muller et al. 2003]. The cornea receives its abundant sensory nerve supply from the ophthalmic division of the trigeminal nerve and to a lesser extent from the maxillary branch of the trigeminal nerve [Muller et al. 2003, Ruskell 1974]. Nerve bundles enter the cornea at the periphery in the middle third of the stroma. At the limbus, these nerves lose their myelin sheath, which is essen-
tial for maintaining corneal transparency [Muller et al. 2003, Oliveira-Soto and Efron 2001]. In the stroma, the nerve bundles run radially towards the corneal apex, where they divide and bend anteriorly. These nerve fibers perforate Bowman’s layer and form the subbasal epithelial nerve plexus, which is located between Bowman’s layer and the basal epithelium [Muller et al. 2003, Oliveira-Soto and Efron 2001, Patel and McGhee 2009]. The subbasal plexus forms a regular dense meshwork with nerve fibers branching both vertically and horizontally between Bowman’s layer and the basal epithelial cells. The axons terminate within the superficial epithelial layers [Muller et al. 1997, Oliveira-Soto and Efron 2001]. Corneal sensitivity has been found to be higher in the center of the cornea than at the periphery [Belmonte et al. 2004, Millodot and Larson 1969].

In addition to corneal innervation, healthy precorneal tear film is also essential for the maintenance of normal corneal function. The precorneal tear film smoothes the minor irregularities of the corneal epithelium, nourishes the cornea, inhibits the growth of micro-organisms on the corneal surface and moistens the corneal epithelium [Riordan-Eva and Whitcher 2008]. Dry eyes are associated with impaired functional visual acuity [Goto et al. 2002]. The precorneal tear film is 35 to 45μm thick [Prydal et al. 1992]. It is composed of three layers; the superficial lipid layer, the middle aqueous layer and the deep mucous layer [Prydal and Campbell 1992]. Both corneal innervation and healthy precorneal tear film play a crucial role in healing processes after ophthalmic surgery.

After the light waves have passed through the cornea, they reach the lens. The power of the lens is one of the three variables determining the refractive power of the eye in addition to the power of the cornea and axial length of the eye. Depending on accommodation, the lens has a refractive power of 10-20 diopters. The iris overlies the lens. The aperture of the iris, the pupil, regulates the amount of light entering the retina. Between the retina and the lens lies the vitreous body. The gelatinous vitreous body consists mainly of water (98%). It supports the intra-ocular tissues and maintains the shape and pressure of the eye. The vitreous body is normally only loosely connected to the retina. If firm local adhesions exist, they expose the eye to retinal detachment as with advanced age, the vitreous body degenerates and separates from the retina.

The optics of the eye create an image on the retina and the retina converts the light ray energy into neuronal impulses. The retina is transparent tissue and lines the fundus of the eyeball. The retina consists of ten distinct layers; the inner limiting membrane, the nerve fiber layer, the ganglion cell layer, the inner plexiform layer, the inner nuclear layer, the outer plexiform layer, the outer nuclear layer, the external limiting membrane, the photoreceptor layer and the retinal pigment epithelium (Figure 3). The structures of the macula of the retina are specialized for high acuity vision. In the middle of the macula lies fovea centralis, where the visual perception is the sharpest. The fovea centralis contains only cones and each cone of
the fovea centralis has its own nerve supply. At the optic disc, located nasally from the fovea, ganglion cell axons exit the retina and form the optic nerve. Because this area lacks photoreceptors, it is also referred to as a “blind spot”.

Figure 3. Layers of the mouse retina. RPE=retinal pigment epithelium; OS=outer segments of photoreceptors; IS=inner segments of photoreceptors; ONL=outer nuclear layer; OPL=outer plexiform layer; INL=inner nuclear layer; IPL=inner plexiform layer; GCL=ganglion cell layer

5.2 VISUAL SYSTEM

The visual system is a part of the central nervous system and makes it possible for people to assimilate information from the surrounding environment. Normal human vision is not a single unitary faculty but rather a synthesis of multiple functional subsystems [Glaser 1999]. The subsystems constantly analyze various aspects of the same retinal image; orientation of line segments, color, motion and depth. It has been postulated that the visual system covers approximately 27% of the cerebral cortex whereas the corresponding value for the hearing system has been postulated to be 8% [Van Essen 2003].

The posterior part of the retina contains the light sensitive specialized neurons called photoreceptors. There are two types of photoreceptors, rods and cones. Rod cells are highly sensitive to light, whereas cones function in bright light and are specialized in color perception [Kahle and Frotscher 2003, Molday 1998]. The cones are concentrated in the fovea centralis, whereas the rods dominate in the peripheral retina. The rods and cones detect the photons of light and respond by producing neural impulses.

Both photoreceptors consist of an inner and outer segment which are connected by a cilium. The inner segments contain the mitochondria, ribosomes and other subcellular organelles. The outer segments of the photoreceptors are located adjacent to the retinal pigment epithelial cell layer and in their membranes lie the photosensitive pigments. The rods contain photopigment rhodopsin and the cones contain three sorts of opsins. Cone opsins are divided into three groups according to the wavelength at which the highest light absorption is observed; blue, green and red cones. [Molday 1998]

The visual cascade is initiated when a photon activates the visual pigment molecule by isomerisation of the chromophore. The chromophore is the part of the molecule that causes a conformational change of the molecule when it falls to light. Isomerisation of the chromophore activates transducin. In the visual cascade, the G-protein transducin activates a phosphodiesterase (PDE), which leads to the hydrolysis of the internal transmitter cGMP to 5’-GMP. The decrease in intracellular cGMP concentration leads to the closure of the cGMP-gated cation channels thus resulting in a membrane hyperpolarization. The hyperpolarization of the photoreceptor leads to a decrease in the release of neurotransmitter glutamate. The release of glutamate from the synaptic terminal is greater in darkness and is reduced in the presence of light. [Molday 1998, Yau 1994]

Visual stimuli are transmitted to the visual cortex via the visual pathway (Figure 4). The visual pathway consists of four neurons. The photoreceptor is the first neuron. The second neuron is the bipolar neuron. Both of the first two neurons are located in the retina. The third neuron is the large ganglion cells, the axons of which combine to form the optic nerve. They extend to the lateral geniculate
nucleus, which is located in the diencephalon and which is the primary processing centre for visual information. The fourth neuron is the geniculate cells. Their axons terminate in the primary visual cortex, which is located around the calcarine fissure in the occipital lobe. [Kahle and Frotscher 2003] In the primary visual cortex, V1, the visual environment is represented retinotopically, i.e. nearby locations on the retina project to nearby points in the cortex, with each visual hemifield being mapped in the contralateral hemisphere. The primary visual cortex is also known as the striate cortex and the areas V2-V5 as extrastriate visual cortical areas.

These multiple visual areas of the cortex are organized into two primary pathways; the ventral and the dorsal pathway. The ventral pathway is associated with recognition, identification of visual stimuli and is often referred to as “what” pathway. The dorsal pathway, commonly referred to as the “where” pathway, is associated with spatial attention and collaborates with movements of the eye and reaching. [Mishkin and Ungerleider 1983, Vanni 2004]
5.3 ANISOMETROPIA

In anisometropia, the refractive power of the eyes is unequal. The reported prevalence of anisometropia varies between 4-30% depending on the study population and definition used [Aine 1984, Anton et al. 2009, Borchert et al. 2010, Hendricks et al. 2009]. Much of this variation can be attributed to different definitions of anisometropia and different ages and types of populations studied. Anisometropia over 4 diopters is present in less than 1% of the population [Lang 2007]. Abrahmson et al. found that although the overall prevalence of anisometropia is relatively stable in the Swedish population, the anisometropia of individual children may increase or diminish during longitudinal observation [Abrahamsson et al. 1990].

Anisometropia can be grouped into five categories depending on the refractive status of the eyes; simple hyperopic anisometropia, compound hyperopic anisometropia, simple myopic anisometropia, compound myopic anisometropia and antimetropia (one eye is myopic, the other hyperopic) [Milder and Rubin 2004]. The tolerance of anisometropia varies widely. As many as two thirds of patients with uncorrected anisometropia will complain of headache and report asthenopic symptoms, while hyperopic anisometropic patients especially tend to have problems with close work and asthenopic symptoms when reading [Milder and Rubin 2004]. A difference in refractive power exceeding 3.0 diopters may result in fusion problems [Milder and Rubin 2004]. Anisometropia causing aniseikonia (a difference in the size or shape of the images on two retinas) is a significant risk factor for the development of amblyopia [Chandna et al. 2001]. The clearer image is favored which may lead to amblyopia in the other eye [Mittelman 2003]. The risk for refractive amblyopia is greater when one eye is more hyperopic than the other [Milder and Rubin 2004]. Amblyopia can also be caused by strabismus, stimulus deprivation, high refractive error or media opacification causing impairment in image quality. In addition to amblyopia and visual discomfort, anisometropia may induce headaches [Holopainen et al. 2005].

5.3.1 CAUSES OF ANISOMETROPIA

Anisometropia may be congenital or iatrogenic. In congenital anisometropia, the reason for the varying development of the two eyes is not known. Congenital anisometropia is known to have hereditary components [Lang 2007]. Iatrogenic anisometropia can be caused, for example, by RRD surgery and other surgical techniques causing a change in the axial length of the eye [Burton et al. 1977, Malukiewicz-Wisniewska and Stafiej 1999, Smiddy et al. 1989]. As the surgery affects the axial length of the eye, the refractive status of the eye may change.
5.3.2 TREATMENT OF ANISOMETROPIA

Spectacles or contact lenses can be used for the correction of defocus and image formation [Curtin 1985]. Often spectacle wearers become symptomatic when there is approximately 3 D of difference in spherical correction. This is because of aniseikonia. Aniseikonia depends both on the degree of refractive errors and the way the refractive error is corrected. The closer to the site of refraction deficit the correction is made, the less difference there is in the retinal image sizes [Lang 2007]. Therefore, contact lenses produce a smaller difference in image size compared to spectacles. In 2000 it was postulated that there are 1.8 billion people who use spectacles [Holden et al. 2000]. Alternatively to spectacles and contact lenses, refractive error can be treated by refractive surgery such as PRK, LASIK or a phakic intraocular lens.

5.4 REFRACTIVE SURGERY AND EXCIMER LASERS

In refractive surgery, the refractive power of the eye is changed by reshaping the curvature of the cornea. During the last two decades, refractive surgery has undergone a significant evolution.

As early as in 1949 Barraquer showed in his thesis that the refractive power of the eye can be changed by reshaping the curvature of the cornea. In 1983, Trokel et al. demonstrated that by using far-UV laser emissions (between 150 and 200 nm), the corneal tissue can be reshaped without causing significant trauma to the tissues adjacent to the cornea [Trokel et al. 1983].

The development of excimer laser was fundamental for present techniques. The term excimer is short for excited dimer. Excited dimers are dimeric molecules formed from two species, at least one of which is in an electronic excited state. Excimer laser typically uses two gases: one inert gas, such as argon, krypton, or xenon, and another reactive gas, such as fluoride. These gas molecules can form an excited dimer under electrical stimulation. When excited dimers decay from the bound upper state to the rapidly dissociating ground state, laser light in the ultraviolet range is produced. Excimer laser can be used for tissue reconstruction because it does not heat the tissue and can remove the intended tissue with microscopic precision. PRK and LASIK are nowadays the dominant procedures in refractive surgery.
5.4.1 PHOTOREFRACTIVE KERATECTOMY (PRK) AND LASEK (LASER ASSISTED SUB-EPIThELIAL KERATOMILEUSIS)

Stephen Trokel was the first to perform PRK in 1983 [Trokel et al. 1983]. In his study of 1983, the operation was performed on freshly enucleated cow eyes. The majority of PRKs are performed to correct myopia. The epithelium is first removed mechanically (with a blunt spatula or brush), chemically or by excimer laser. The laser beam is then focused on the anterior stroma and the excimer laser photodissolution consists of the epithelium, subbasal nerves, Bowman’s layer and variable depth of stromal tissue (Figure 5). The depth of ablation depends on the magnitude of dioptic correction.

Figure 5. Illustration of PRK [Reprinted from www.pacificvision.org with the permission of the Pacific Vision Institute, San Francisco]

Postoperative pain is one of the most important drawbacks of PRK. PRK treated eyes are significantly more painful during the first days after RS than eyes that have undergone LASIK [El-Maghraby et al. 1999, Slade et al. 2009]. Severe pain lasts 12 to 24 hours and is followed by irritation and tear secretion until epithelial coverage is complete after 48 to 72 hours [El-Maghraby et al. 1999, Fagerholm 2000]. Haze (stromal opacity) is also associated with wound healing after PRK [Lee et al. 2001, Lohmann et al. 1991, Moller-Pedersen et al. 2000] but has been shown to diminish with time [Rajan et al. 2004]. There is a higher risk of postoperative haze (stromal opacity) and less predictable refractive results if higher corrections are attempted using PRK [Seiler et al. 1992, Shah et al. 1998, Taylor et al. 1996]. In the study by Taylor et al. the predictability of refraction and visual acuity decreased progressively with increasing myopia [Taylor et al. 1996]. On the other hand, refractive stability achieved at one year has been shown to be maintained up to 8-12 years with no late regression [Rajan et al. 2004, Zalentein et al. 2010].

Long term studies of PRK have shown that it is a safe and predictable procedure in correcting low and moderate refractive errors [O’Connor et al. 2006, Rajan et

For thin corneas, PRK may be preferable to LASIK because of the probable preservation of the mechanical stability of the cornea. The safety of the procedure in the absence of flap complications is one of the reasons why some surgeons favor PRK.

In 1999 a modification of PRK, called LASEK (Laser Assisted Sub-Epithelial Keratomileusis) was introduced. In LASEK, the corneal epithelium is loosened with alcohol and the epithelial flap is pushed aside in order to reshape the cornea as it is done in PRK. The epithelium is then replaced and held in place with a soft contact lens. Since the introduction of LASEK, there has been controversy whether or not it has advantages over LASIK or PRK [Ambrosio and Wilson 2003, Ghanem et al. 2008, Scerrati 2001].

5.4.2 LASER IN-SITU KERATOMILEUSIS (LASIK)

LASIK is currently the most common procedure in refractive surgery [Duffey and Leaming 2005, Sandoval et al. 2005]. As with PRK, the majority of LASIK procedures are performed to correct myopia. In LASIK, a corneal flap of 100-200μm is created with a microkeratome or a femtosecond laser. The corneal flap consists of the epithelium, the subbasal nerve plexus and the anterior stroma. After the flap has been lifted, the excimer laser is focused on the exposed stromal tissue. In LASIK, the ablation is accordingly done in the stromal bed beneath a hinged corneal flap. During the operation, the eye is immobilized with a suction ring. The stromal bed is irrigated and the corneal flap repositioned, without sutures, after laserablation.

![Figure 6. Illustration of LASIK](www.pacificvision.org)
The main advantage of LASIK over PRK is related to maintaining the central corneal epithelium therefore causing less discomfort and pain after the procedure [Ambrosio and Wilson 2003]. On the other hand, the risk for complications during the preparation of the corneal flap has diminished the enthusiasm as the complications can be sight threatening [Melki and Azar 2001, Stulting et al. 1999].

LASIK has the advantage of fast, painless recovery [El Danasoury et al. 1999, El-Maghraby et al. 1999]. Visual acuity is often regained in one day. There is also less if any stromal haze formation after LASIK because there is no epithelial-stromal interaction [El-Maghraby et al. 1999, Ivarsen and Moller-Pedersen 2005]. On the other hand, LASIK patients complain of dry eye symptoms relatively frequently [Melki and Azar 2001, Sugar et al. 2002] owing to the slow regeneration of the corneal nerves [Moilanen et al. 2008]. Corneal ectasia is a severe but rare complication of LASIK and it can often be avoided by leaving the residual stromal bed thick enough [Melki and Azar 2001]. The current consensus is a minimum of 250 μm, but the safe limit of residual stromal bed thickness after refractive surgery remains subject to speculation. Many ophthalmic surgeons prefer 300 -350 μm to avoid corneal ectasia.

The long-term results of LASIK have been encouraging [Condon et al. 2007, Kymionis et al. 2007, O’Doherty et al. 2006, Sekundo et al. 2003, Zalentein et al. 2009]. O’Doherty et al. concluded in 5-year follow up that LASIK offers predictable results in terms of refractive and visual outcome with mild regression in refraction over time [O’Doherty et al. 2006]. Zalentein at al. studied 38 eyes of 21 patients undergoing LASIK surgery [Zalentein et al. 2009]. They all were invited for ophthalmological examination 7 - 8 years after surgery. Seven to 8 years postoperatively myopic regression was observed as 42% of the patients were within ±1.0 D of the intended correction. Patient satisfaction was found to be high with 100% concluding that they would have LASIK surgery again.

In the long run, PRK and LASIK have been found to be equally effective, predictable, stable and reasonably safe [El Danasoury et al. 1999, El-Maghraby et al. 1999, Hersh et al. 1998, Miyai et al. 2008, Shortt and Allan 2006] and good patient satisfaction has been obtained with both procedures [Bailey et al. 2003, Brunette et al. 2000]

5.4.3 OUTCOMES OF REFRACTIVE SURGERY ON MYOPIC PATIENTS

Most RS procedures are performed on myopic patients with low to moderate degree of myopia [Sakimoto et al. 2006]. The results of RS on this patient population are excellent. Sakimoto et. al conducted an extensive review of the present RS results [Sakimoto et al. 2006]. Their review revealed that 94-96% of LASIK patients with low to moderate myopia achieved the attempted correction within ± 1 D. Si-
milarly, UCVAs were 20/40 or better in 95-96% of these patients postoperatively. In 67 -72% of the patients, UCVA was found to be 20/20 or better. In the review by Sakimoto et al. (2006), combining all levels of myopia, 90% of both PRK and LASEK patients achieved the attempted correction within ± 1 D. UCVA was found to be 20/40 or more in 94% of PRK patients and in 95% of LASEK patients. The corresponding values for UCVA 20/20 or better were 61% and 74%. In general, the results of treating high myopia with RS are expected to be less predictable as more tissue removal is required. This was also found in the review by Sakimoto et al (2006). In LASIK patients, the attempted correction was achieved within ± 1 D in 79-80 % of patients with high myopia (preoperative SE -7D to -12D). Of these patients 89-94% had UCVA of 20/40 or better but only 48-64% of these patients achieved UCVA of 20/20 or better.

5.5 OUTCOMES OF REFRACTIVE SURGERY ON ANISOMETROPIE PATIENTS

To the best of our knowledge, only two groups have reported the effect of refractive surgery on adult anisometropic patients. So far there has been no widespread interest in studying the treatment of adults’ visual deficiencies because it is thought that the visual system is only sufficiently plastic for cortical modifications during the first decade of life. Maden et al. followed anisometropic adult patients for > 12 months [Maden et al. 1998]. In their study, BSCVA increased in 7 (35%) eyes, remained the same in 12 (60%) eyes and decreased in 1 eye (5%). Unfortunately, the study lacked statistical analysis. Holopainen et al. showed in a small retrospective series of 11 adult anisometropic patients that unilateral PRK performed for myopic anisometropia may improve patients’ visual performance in terms of contrast sensitivity [Holopainen et al. 2004]. No statistically significant improvement in BSCVA was found. Contrary to adult anisometropic patients, the use of refractive surgery on anisometric children has been widely studied [Alio et al. 1998, Astle et al. 2002, Autrata and Rehurek 2004, Magli et al. 2008, Paysse et al. 2004, Paysse et al. 2006, Rashad 1999]. Paysse et al. found that PRK can be safely performed on anisometric children and they also found that visual acuity and stereopsis improved despite several children being beyond the considered standard age of visual plasticity [Paysse et al. 2004]. Paysse et al. studied this same sample of patients later (mean last follow-up 31 months postoperatively) and found that PRK in these children resulted in stable reduction in refractive error and improvement in visual acuity [Paysse et al. 2006]. The same was found by Autrata et al. in their 2-year follow-up [Autrata and Rehurek 2004]. They compared the result
of PRK in children to conventional treatment of myopic anisometric amblyopia. Visual acuity and binocular vision outcomes were found to be better in children who received permanent surgical correction of anisometropia than in those treated conventionally with contact lenses.

5.6. VISUAL IMPAIRMENT

Amblyopia is a developmental defect of visual processing. It results in a reduction of the best spectacle corrected visual acuity despite the eye being physically normal [Attebo et al. 1998]. Amblyopia is often defined as two or more Snellen or logMAR lines difference between eyes in BSCVA. Besides reduced visual acuity, an accentuation of the crowding phenomenon is typical for amblyopic patients [Levi 2008, Yanoff and Duker 2004]. Crowding impairs the ability to discern objects in a larger array, while single objects are recognized more easily.

Amblyopia affects between 1-3 % of the population [Attebo et al. 1998, Brown et al. 2000, Eibschitz-Tsimhoni et al. 2000, Williams et al. 2003]. Amblyopia can be divided into three groups; anisometric, strabismic and stimulus deprivation amblyopia. In all these forms of amblyopia, the defects may be explained by the mechanism of lack of use of the other eye.

In anisometric amblyopia, the eye with the greater refractive error is suppressed. A difference in refractive power exceeding 3 diopters (D) leads to suppression of the other eye and the depth of amblyopia is proportional to the degree of anisometropia. Anisometric amblyopia is common in anisometric hyperopes and unilaterally high myopes [Yanoff and Duker 2004]. In strabismic amblyopia abnormal vision develops in the deviating or strabismic eye due to abnormal binocular interaction. The strabismic eye does not develop a normal functional connection with the visual centers of the brain. Amblyopia is more common in esotropia than in exotropia [Riordan-Eva and Whitcher 2008]. The amount of visual impairment of the strabismic eye is proportional to the fixational preference shown to the other eye [Yanoff and Duker 2004]. In stimulus deprivation amblyopia, the image focused on the retina is chronically blurred. Underlying causes include, for example, congenital or early-onset cataract and corneal opacity from glaucoma or dystrophy.

The treatment modalities of amblyopia include refractive correction by spectacles or contact lenses and/or occlusion therapy with patching of the dominant eye. Atropine penalization of the sound eye may also encourage the amblyopic eye to work better [Pediatric Eye Disease Investigator Group. 2002, Wu and Hunter 2006]. The results of these conventional treatment methods may not always be permanent, however [Bhola et al. 2006, Holmes et al. 2004, Holmes et al. 2007,
Moseley et al. 1997]. Recently, Holmes et al. found that the recurrence rate of amblyopia was about 25% [Holmes et al. 2007].

It seems that neuronal networks in the primary visual cortex of amblyopic patients are functionally abnormal [Polat 1999], but abnormalities have also been found in the lateral geniculate body [von Noorden and Crawford 1992]. Functional magnetic resonance imaging studies show reduced activation of the cortex after stimulation of the amblyopic eye [Algaze et al. 2002, Barnes et al. 2001, Conner et al. 2007, Goodyear et al. 2000, Liu et al. 2004, Muckli et al. 2006].

5.7 RETINAL DETACHMENT

In retinal detachment, the neurosensory retina separates from the underlying retinal pigment epithelium (RPE). The incidence of retinal detachment is approximately 12 per 100,000 population per year [Yanoff and Duker 2004]. Although retinal detachment is rather unusual in general population, it can be sight-threatening unless treated properly and early enough. If the macula detaches, some degree of vision loss always persist despite successful surgery.

Retinal detachments can be divided into three groups; rhegmatogenous retinal detachment, tractional retinal detachment and exudative retinal detachment. Rhegmatogenous retinal detachment (RRD) is the most common form of retinal detachment. In RRD, the neural retina separates from the underlying RPE because of a tear in the retina. The fluid from the vitreous cavity can therefore move into the subretinal space and separate the two layers. Fortunately, most retinal breaks do not lead to retinal detachment as approximately 7% of adults have retinal breaks [Lang 2007]. High myopia increases the risk of RRD. Typically posterior vitreous detachment precedes RRD and the retinal breaks form at the sites of significant vitreoretinal adhesions. In tractional retinal detachment, the sensory retina is pulled away from the RPE by the tensile forces of the vitreous structures. The most important predisposing disease is proliferative diabetic retinopathy. In exudative retinal detachment, subretinal fluid accumulates under the neurosensory retina. Underlying causes include, for example, subretinal neovascularisation and choroidal tumors.

The symptoms of retinal detachment with preceding posterior vitreous detachment are flashes of light, floaters, lightdark shadow in the visual field/peripheral visual field defect which may be progressive. If the intraocular media is clear, the diagnosis of retinal detachment can be made on the basis of clinical examination. In case of intraocular opacities, ultrasonography can be of help in the diagnostics.
Small retinal tears and detachments can be treated with laser photocoagulation or cryotherapy. Both procedures create adhesions between the RPE and the sensory retina to prevent the retinal detachment from spreading. In scleral buckle surgery, an inward indentation of the sclera is created by sewing one or more silicone bands to the sclera. This indentation maintains the retina in position and relieves vitreoretinal traction. Cryotherapy is used to close the retinal breaks prior to the placement of the buckle. In vitrectomy, the vitreous gel is removed and replaced with gas or silicone oil. These fluids press the sensory retina back into contact with the RPE. In pneumatic retinopexy, laser or freezing treatment is applied to the retinal hole and an intravitreal expanding gas is injected into the vitreous cavity. The gas bubble reattaches the retina. Postoperative posturing may be required.

Scleral buckling surgery often increases the axial length of the eye and therefore the eye becomes more myopic [Beekhuis et al. 1993, Larsen and Syrdalen 1979, Malukiewicz-Wisniewska and Stafiej 1999, Smiddy et al. 1989]. Anisometropia may develop because of axial lengthening of the other eye.

The correction of refractive errors induced by RRD surgery has been studied earlier [Barequet et al. 2005, Belda et al. 2003, Bilgihan et al. 2000, Farvardin et al. 2006, Sforza and Saffra 2003, Sinha et al. 2003] but there is a lack of long-term follow ups.

### 5.8 MULTIFOCAL FMRI

Functional magnetic resonance imaging (fMRI) is a powerful neuroimaging technique which has become a dominate method in the brain mapping field because of its absence of radiation exposure, relatively wide availability and noninvasiveness. Another advantage of fMRI is its high spatial resolution. Functional magnetic resonance imaging technique is based on the connection between neural activity and increased energy metabolism.

An increase in neuronal activity is associated with increased local blood flow [Logothetis et al. 2001] and blood oxyhemoglobin concentration follows monotonically and rather linearly the flow. Because oxyhemoglobin is diamagnetic and deoxyhemoglobin paramagnetic, the oxyhemoglobin disturbs the T2* weighted MR signal less than the deoxyhemoglobin. Ogawa et al. were the first to discover blood-oxygenation-level-dependent (BOLD) MRI contrast in 1990 [Ogawa et al. 1990]. Blood-oxygenation-level-dependent fMRI response increases parallel with the concentration of oxygenated hemoglobin and therefore with the increasing synaptic activity.

Vanni et al. developed a multifocal mapping method for fMRI (mffMRI) [Vanni et al. 2005]. Multifocal fMRI allows parallel signal acquisition from multiple lo-
cal visual field representations in the cortex in reasonable measurement time. In mffMRI, multiple fixed regions are stimulated concurrently with an independent temporal activation pattern for each region. Each region in the multifocal stimulus evokes a spatially localized fMRI activation pattern (see Figure 3 and 4 of Study IV). As each region has an independent representation sequence, the resulting compound response can be decomposed into components, one for each stimulus region.

In the mffMRI stimulus, the visual field is divided into 61 regions (see Figure 1 a in (IV)). In order to stimulate approximately equal areas within cortical area V1, the regions in the stimulus are scaled according to the human magnification factor. Region number 61 corresponds to the stimulation of the fovea. Figure 1b in IV presents an example frame of the 61-region mffMRI stimulus. In the stimulus, half of the 61 visual field regions are concurrently active and the rest of the regions inactive. Figure 1c in IV shows the 61-region dartboard as a rectangular grid. This rectangular grid is used in the representation of mffMRI data results. Region 61 is absent because the analysis of the foveal data was done separately from the rest of the 60 regions.
6 AIMS OF THE STUDY

The present study was designed to investigate the functional outcome of excimer laser refractive surgery on adult anisometropic and visually impaired patients. In addition, we examined changes in the primary visual cortex (V1) of anisometropic and isometropic myopic patients using mffMRI after excimer laser refractive surgery.

The specific aims were as follows:

1. To study the effect of refractive surgery on adult anisometropic patients and to test the hypothesis that anisometropic adult patients suffer from mild sensory suppression which might be reversed by using refractive surgery (I).
2. To evaluate the long-term effects of refractive surgery on patients with a history of operated RRD and iatrogenic anisometropia (II).
3. To study the visual and refractive outcome of refractive surgery on visually impaired adult patients (III)
4. To study the changes in the primary visual cortex (V1) of adult anisometropic patients and isometropic myopic patients after refractive surgery using mffMRI.
7 SUBJECTS AND METHODS

7.1 SUBJECTS

The study was carried out according to the tenets of the Helsinki Declaration. The research plans were all accepted by the Ethical Review Committee of Helsinki University Central Hospital.

7.1.1 ANISOMETROPIC PATIENTS AND THEIR CONTROLS (STUDY I)

Eighty-seven patients with myopic anisometropia were found, and 57 of them were included in the study (42 women and 15 men; mean age 33±8.1 years, range from 18 to 58 years). Because of inadequate follow-up data or because of postoperative complications which decisively affected the visual performance, 30 anisometropic patients were excluded from the analysis. None of the patients were amblyopic by the definition of preoperative BSCVA being ≤20/40 (≤ -0.3 on a LogMAR scale). Thirty-three anisometropic patients underwent bilateral refractive surgery during our data collection period but only the more myopic eye was included in our analyses. Some of the anisometropic patients who had had only one eye operated on during our data collection time had the other eye operated on later.

In the control group there were 174 subjects with isometropic myopia (124 women and 50 men; mean age 31±7.3 years, range from 16 to 52 years). Bilateral refractive surgery was performed on 43 controls and the rest of them had only one eye operated on. Therefore 217 control eyes were included in the analysis. Some of the control subjects who had only one eye operated on during our data collection period, had the other eye operated on before or after our data collection period.

7.1.2 RRD PATIENTS (STUDY II)

Since February 1990, patients with a history of treated RRD and subsequent refractive surgery were scored from the records of Helsinki University Eye Hospital. Minimum time elapsed after refractive surgery was set at 40 months and on these
bases ten patients (ten eyes) were found. Six of them were women and four of them were men. Eight of the eyes were left and two were right. These patients were invited for an ophthalmological re-examination. The mean age of the patients at the time of RRD was 35±12 (range 20 to 57 years).

7.1.3 VISUALLY IMPAIRED PATIENTS AND THEIR CONTROLS (STUDY III)

In this study, a patient was considered visually impaired if his/her preoperative BSCVA on a LogMAR scale was ≤-0.1 (on Snellen scale ≤0.8). From a refractive surgery database comprising 1,716 patients with a history of PRK or LASIK, visually impaired patients were scored. Altogether 96 visually impaired patients were found. Controls for these patients were collected from the same database. Controls had preoperative BSCVA > -0.1 (Snellen >0.8) (n=174).

Study III consisted of two parts. In the first part, out of those 96 patients who were visually impaired, the patients with follow-up visits preoperatively and 5-7 months, 8-13 months and 14-24 months postoperatively were included (n=11). They were all treated with PRK. Controls treated with PRK and followed up identically were sought (n=9) These 11 visually impaired patients and 9 control subjects formed cohort 1. Five of the patients and four of the controls of cohort one were men. Seven of the visually impaired eyes and five of the analyzed control eyes were left.

In the second part of the study, visually impaired patients with a follow-up visit preoperatively and 14-24 months postoperatively were selected (n=41) and the same was done for control subjects. Fifty-four control subjects were found. These 41 visually impaired patients and 54 control subjects formed cohort 2. Seventeen of the patients and 16 of the controls in cohort 2 were men. Twenty-one of the visually impaired eyes and 29 of the analyzed control eyes were left. Both in cohort 1 and 2, only one eye of each patient and control was included in the data analysis.

7.1.4 PATIENTS AND CONTROLS ATTENDING FMRI STUDY (STUDY IV)

Two anisometropic patients and two isometropic myopic patients were recruited for the study before their refractive surgery operation. In addition, two healthy control subjects without refractive surgery attended fMRI measurements at the beginning and at the end of the study.
Anisometropic and isometropic myopic patients were all women (mean age at the time of RS 33 years, range 24-46 years). Patients 1 and 2 were anisometropic and patients 3 and 4 myopic. Preoperatively, the anisometropic patients suffered from anisometropia of 6.6 and 4.7 D. Attempted correction ranged from 3.9 to 4.6 D in the anisometropic group and from 1.8 to 7.9 D in the myopic group.

7.2 METHODS

7.2.1 STUDY PROTOCOLS

7.2.1.1 Study I
Both anisometropic patients and control subjects were treated either with PRK or LASIK. To study the effect of refractive surgery on these patients, both anisometropic patients and myopic controls were examined preoperatively and 1, 3, 5-7, 8-13 and over 24 months postoperatively. Anisometropic patients were operated on at the Helsinki University Eye Hospital between November 1999 and April 2002. Forty-four (77%) of the anisometropic eyes operated on were operated on using PRK and 13 (23%) using LASIK. Control subjects were operated on at the same hospital between September 1995 and March 2004. One hundred and twenty four (57%) of the control eyes were operated on using PRK and 93 (43%) using LASIK. For some patients and control subjects there was more than one follow-up at 5-7 months and 8-13 months postoperatively. If this was the case, the follow up visit with the highest BSCVA was noted.

7.2.1.2 Study II
The patient histories for the ten patients with a history of RRD treatment and subsequent refractive surgery were obtained. Preoperative and postoperative evaluation, concerning both RRD surgery and refractive surgery operation, had included in these patients the assessment of UCVA and BSCVA, assessment of subjective and objective refraction, slitlamp microscopy, indirect ophthalmoscopy and applanation tonometry. In addition, all patients had had corneal computed topography
(TMS-2N Topographic Modelling System, Tomey) before and after the refractive surgery. Retinal detachment in these patients had been treated with standard surgical techniques. Five of the patients were treated with encircling silicone band, two patients with scleral buckle and three patients with both of these. Six patients had had additional cryocoagulation of retinal breaks. Nine out of ten patients had had one surgical operation for RRD. One patient had been operated on again because of persistent RRD. One patient suffered from persistent periorcular pain after RRD surgery and the silicone band was therefore removed 4 months postoperatively. One of the RRD patients had an RRD involving the macula. Refractive surgery was performed on these patients at the Helsinki University Eye Hospital between January 1999 and June 2002. The same surgeon operated on all these patients. Six of them were treated with PRK and four patients with LASIK. Postoperative treatment after refractive surgery has been described in Study II.

At the ophthalmologic re-examination (mean 67±14 months after the refractive surgery) a complete ocular and medical history was obtained from each patient. Examination included assessment of UCVA and BSCVA, assessment of refraction, slitlamp biomicroscopy and applanation tonometry.

7.2.1.3 Study III

All patients and controls were operated on at the Helsinki University Eye Hospital between May 1996 and September 2002. Both the preoperative and postoperative evaluation of patients and controls included assessment of UCVA, BSCVA, cycloplegic refraction and applanation tonometry. In cohort 1, the follow-ups were preoperatively and 5-7 months, 8-13 months and 14-24 months postoperatively. In cohort 2, patients and controls had ophthalmological examination preoperatively and 14-24 months postoperatively. In cohort 1, all patients and controls were treated with PRK. In cohort 2, 38 of the visually impaired patients were treated with PRK and 3 patients with LASIK. Out of 54 control subjects of cohort 2, 31 were treated with PRK and 23 with LASIK.

7.2.1.4 Study IV

Both anisometropic patients were operated on using PRK as well as the other myopic patient. Patient 4 had LASIK. To correct anisometropia, only the more myopic eye of the anisometropic patients was operated on. Isometropic myopic patients had
both eyes operated on. All four patients were operated on between April and November 2005 at the Helsinki University Eye Hospital by the same surgeon as the patients in Study II.

The mffMRI was measured preoperatively and at three, six, nine and twelve months after the refractive surgery. Patient number 2 became pregnant during follow-up and hence her follow-up visits at three, six and nine months postoperatively had to be cancelled. This patient was therefore examined with mffMRI preoperatively and 12 and 29 months postoperatively instead of the planned follow-up schedule. Before each mffMRI measurement, each patient attended an ophthalmological examination. The examination included the assessment of visual acuity and manifest and cycloplegic refraction and contrast sensitivity, biomicroscopy to exclude any pathology that could affect the corneal wound healing process, corneal pachymetry, videokeratography (Tomey, TMS – 2N Topographic Modelling System Version 2.4.2J), wave front analysis (VisX Customvue analysis system), and mydriatic funduscopy.

Functional MRI was obtained with a 3-T GE Signa (General Electric Medical Systems, Milwaukee, WI, USA) scanner using an eight-channel phased array head coil. During mffMRI measurement, spectacles were used to correct each patient’s and control’s refraction. The patients and controls watched the stimuli mono-ocularly from a distance of 35 centimeters. The same stimuli were presented separately to the left and right eye (see Figure 1 b in IV). Patients were advised to fixate precisely on a point in the middle of a gray display. A run of one functional series lasted 8 minutes 22 seconds and consisted of 68 blocks. Within blocks of 7 sec, half of the regions were concurrently active and the rest of the regions inactive. Matlab (The MathWorks Inc., Natick, MA) was used to generate the stimulus images. Presentation software (Neurobehavioral Systems Inc., Albany, CA) was used to control the display of the stimuli during the functional runs.

The stimuli were presented via a back projector system, with a Christie X3 (Christie Digital Systems) data projector comprising three micromirrors. The data projector comprised three micromirrors to make the stimulus visible to the patients and controls as they lay in the MRI tube. Two functional series were performed mono-ocularly for each eye. T1-weighted scans were acquired for anatomical reference after the functional series. For functional imaging, the single-shot gradient-echo echo-planar imaging sequence had the following parameters: repetition time, 1819 ms; echo time, 30 ms; flip angle, 60°; acquisition and reconstruction matrices, 64x64; field of view, 160x160mm, and slice thickness 2.5 mm.

Altogether 24 slices thickness 2.5 mm were obtained. They were acquired without gap in interleaved order in order to minimize the influence of excitation pulses upon adjacent slices. To cover the V1, the slices were oriented perpendicular to the parieto-occipital sulcus. For each functional run, the first four scans were
discarded. This is a standard method when analyzing fMRI data. The rejection of the first four scans is done because the MR signal is greatest in the first images, as the magnetization has not yet reached steady state [Huettel et al. 2004].

As mentioned earlier, the stimulus consisted of 61 separate regions. A cluster was defined for each of the 61 regions of the stimulus (p_fwe <0.05 and three as the minimum number of voxels). As the 61 clusters were also defined for each of the two eyes of anisometropic patients, myopic patients and control subjects at each of the 22 sessions, it resulted in 61*2*22 = 2684 data points. Outliers and visual field regions with no signal were discarded. A data point was regarded as an outlier if the distance between the cluster’s strongest voxel and the location of the corresponding voxels in the local neighborhood exceeded 35 mm. Noise and residual head motion after motion correction, for instance, may cause outli

7.2.2 STATISTICS

7.2.2.1 Study I

The independent samples t test (SPSS version 12.0.1; SPSS Inc, Chigago III) was used to compare the pre- and postoperative levels of visual acuity in anisometropic patients and control subjects. A paired samples t-test (SPSS version 12.0.1) was used to compare visual acuity changes as a function of time within the group: separately among anisometropic patients and control subjects.

7.2.2.2 Study II

The change in the mean BSCVA of patients with a history of RRD surgery and subsequent refractive surgery was analyzed using the analysis of variance for repeated measures with post hoc Bonferroni-Dunn correction.

7.2.2.3 Study III

Statview (Version 5.0.1, SAS Institute Inc) was used to perform the statistical analysis of Study III. To analyze cohort 1, ANOVA with Bonferroni adjustments for repeated measures was first carried out. After that, the analysis with two tailed
Paired t-test corrected for repeated measures was done. In cohort 2, the unpaired two-tailed t-test was used to compare the visual acuity data between visually impaired patients and control subjects. For the t-test analysis the level of significance was set at $p < 0.05$.

7.2.2.4 Study IV

Functional MRI data was first converted to SPM (statistical parametric mapping) analyze format. SPM2 software (The Wellcome Trust Centre for Neuroimaging, London, England; http://www.filion.ucl.ac.uk/) was used for the preprocessing of the data. Preprocessing is a crucial and standard method in the analysis of fMRI data. The goal of preprocessing is to correct for non-task related variability in the data [Huettel et al. 2004]. For example, it diminishes the disturbances of the data caused by head motion. In addition to standard head motion correction, standard slice timing correction was applied. Motion correction parameters were included as confounds in the design matrix. We did not smooth our data because exact spatial information was essential.

Using SPM2 statistical estimation, model parameters corresponding to % signal change for each region were obtained. The % signal change in the BOLD fMRI response was first calculated separately for each voxel, and then the mean value for each significant cluster of voxels. Analysis of the fovea was done separately from the rest of the 60 regions.

A map of t statistics termed the SPM(t) was obtained by dividing each point of the activation map by the corresponding standard error. Figure 3 of Study IV shows a single region activation SPM(t) maps for patients 2 and 3 and control 1. The map indicates the significance of activation in each region.

The mffMRI responses can also be visualized on the cortical surfaces (see Figure 4 of Study IV). The white and gray matter borders of the cortex can be segmented and reconstructed from the individual anatomical MRI images using Freesurfer software package [Dale et al. 1999].
8 RESULTS

8.1 VISUAL ACUITY AND REFRACTION

8.1.1 STUDY I

Among anisometropic patients the mean preoperative SE was -7.20±2.40 D (range -13.375 to -3.25 D) and the mean SE attempted correction was 7.00±2.4 D (range 3.125 to 13.375 D). For control subjects the mean preoperative SE was -6.4±1.9 D (range -13.375 to -3.125 D) and the mean SE attempted correction was 6.30±1.9D (range 2.9 to 12.90 D). The mean preoperative BSCVA was -0.0143±0.0572 (0.98±0.12 on Snellen scale) in anisometropic patients and in control subjects 0.0136±0.0361 (1.04±0.09 on Snellen scale). The mean preoperative BSCVA was found to be significantly higher for control subjects than for anisometropic patients (p=0.001). The mean BSCVA of the control group remained better across the follow-up time but its statistical significance declined over time.

The mean follow-up time for the anisometropic patients was 25±14 months and 26±14 months in the control group. In the control group, statistically significant improvement in BSCVA was found three months postoperatively while among anisometropic patients the time needed for significant improvement in BSCVA was 8-13 months. In other words, the improvement in BSCVA behaved very differently in anisometropic patients compared to control subjects (see Figure 3 of (I)).

8.1.2 STUDY II

Preoperatively before RRD surgery, mean SE was -6.8±4.0 D (range -12.25 to 0.00) and mean anisometropia was 2.6±2.6 D (range 0.00 to 7.50 D). As expected, the
RRD surgery increased both SE and degree of anisometropia. After RRD surgery, mean SE was $-9.2 \pm 3.2$ D (range -13.5 to -2.5 D) and mean degree of anisometropia had increased to $4.2 \pm 2.8$ D (range 0.00 to 8.25). Before RRD surgery, mean BSCVA was $-0.17 \pm 0.22$ (Snellen 0.75±0.30), range -0.5 to 0.0 (Snellen 0.32 to 1.00). A mean of 40 ±45 months after RRD surgery, the mean BSCVA was $-0.07 \pm 0.14$ (Snellen 0.89± 0.24) range -0.4 to 0.1 (Snellen 0.4 to 1.25). This improvement in BSCVA was found to be statistically insignificant ($p = 0.04$).

The average time between RRD surgery and refractive surgery was $40 \pm 45$ months (range 6 to 126 months). The mean attempted correction was $5.9 \pm 2.9$ D (range 1.63 to 11.25 D). Before refractive surgery, the mean corneal thickness ranged from 452 to 580 μm. Refractive surgery was performed to good effect in all patients; none of the patients had any intra- or postoperative complications.

At the ophthalmological re-examination 67±14 months after RS, mean SE was $-3.4 \pm 2.4$ D (range -8.125 to -0.25 D) and mean anisometropia had decreased to $1.2 \pm 0.7$D (range 0.00 to 2.75 D). A statistically significant improvement in BSCVA was also found ($p=0.01$). Mean BSCVA had improved to $-0.04 \pm 0.12$ (Snellen 0.94±0.25), range -0.2 to 0.1 (Snellen 0.63 to 1.25). The BSCVAs before and after refractive surgery did not differ significantly. At this last follow-up, mean corneal pachymetry was 463 ± 58 μm (range 360 to 561 μm).

Five out of 10 patients were within ±1.00 D of the attempted correction and 9 patients were within 2.00 D of the attempted correction 1 month after refractive surgery. At the ophthalmological re-examination 67±14 months postoperatively, 6 patients were within ±1.00 D of the attempted correction and 7 were within ±2.00 D.

### 8.1.3 STUDY III

#### Visual acuity

**Cohort 1**

The development of BSCVA in both visually impaired patients and control subjects of cohort 1 is shown in Figure 3 (III). Preoperatively the mean BSCVA among visually impaired patients was $-0.15 \pm 0.13$ (Snellen 0.73±0.16), range -0.52 to -0.10 (Snellen 0.30 to 0.80). The mean BSCVA of visually impaired patients had reached the level of $0.05 \pm 0.04$ (Snellen 1.13±0.10) 14-24 months after the refractive surgery, range 0.00 to 0.08 (Snellen 1.0 to 1.2). Among control subjects, mean preoperative BSCVA was $0.04 \pm 0.02$ (Snellen 1.11±0.17), range 0.00 to 0.18 (Snellen 1.00 to 1.50). 14-24 months after the refractive surgery, mean BSCVA in the control group was
0.05±0.08 (Snellen 1.13±0.21), range -0.05 to 0.18 (Snellen 0.9 to 1.5). Statistically tested, there was no significant improvement in BSCVA among control subjects at any follow-up point, but for visually impaired patients BSVA was already found to be significantly improved at the first follow-up point 5-7 months postoperatively. This improvement remained significant throughout the follow-up time (p<0.001). As shown in Figure 3 (III), the difference in mean BSCVA between visually impaired patients and control subjects diminished over time. Statistically tested, the BSCVA of the controls was found to be significantly better than that of the visually impaired patients only before the refractive surgery. In cohort 1, nine of those 11 visually impaired patients and all control subjects were found to be within 1 D of the attempted correction 14-24 months postoperatively.

Cohort 2
Preoperatively the mean BSCVA among visually impaired patients was -0.15±0.12 (Snellen 0.74±0.14), range -0.70 to -0.10 (Snellen 0.20 to 0.80). The mean BSCVA of visually impaired patients had reached the level of 0.02±0.07 (Snellen 1.06±0.16), range -0.22 to 0.18 (Snellen 0.6 to 1.5) 14-24 months after the refractive surgery. Among control subjects, mean preoperative BSCVA was 0.01±0.03 (Snellen 1.04±0.10), range -0.05 to 0.18 (Snellen 0.90 to 1.50). The mean BSCVA in the control group was 0.06±0.06 (Snellen 1.15±0.16), range -0.05 to 0.18 (Snellen 0.9 to 1.5) 14-24 months after the refractive surgery. This improvement in BSCVA was found to be statistically significant both among visually impaired patients and control subjects. Contrary to cohort 1, BSCVA was found to be significantly better both preoperatively and 14-24 months postoperatively among control subjects although its statistical significance diminished after refractive surgery. In cohort two, 32 of 41 (78%) visually impaired patients and 47 of 52 (90%) control subjects were found to be within ±1 D of the attempted correction 14-24 months postoperatively.

The minimum level of preoperative BSCVA for the refractive surgery to be effective was not established. The three most visually impaired patients in cohort 1 had preoperative BSCVAs of -0.7 (Snellen 0.2), -0.5 (Snellen 0.3) and -0.4 (Snellen 0.4). The first one gained seven lines of Snellen visual acuity, the second gained six lines and the third gained four lines.

8.1.4 STUDY IV

The patients’ pre- and postoperative refraction (in spherical equivalent) and best-spectacle-corrected visual acuities (BSCVA) are shown in Table 1 (IV). BSCVA imp-
roved in both operated anisometropic eyes. In anisometropic patients attempted correction was achieved within ±1 D 12 months postoperatively in patient 1 but not in patient 2. Both myopic patients attained their attempted correction within ±1 D 12 months postoperatively.

8.2 MFMRI RESULTS

Statistically significant signal was measured on average from 81% of V1 regions in both anisometropic and myopic patients. In controls, the corresponding value was 73% (see Figure 5a (IV).

In anisometropic patients the mean percentual BOLD fMRI responses from the 60 regions in V1 ranged during follow-up from 1.0 % to 1.3%. In myopic patients the corresponding values were 0.8 and 1.4 % and in controls 1.1% and 1.5%. As shown in Figure 5b (IV), there were no significant changes in mean BOLD fMRI response strength during follow-up. When studied separately in each patient and control, there were no changes over time in within-subject difference between eyes BOLD responses (operated vs unoperated eye in anisometropic patients and left versus right eye in myopic patients and controls) (Figure 5 c (IV)).

In Study IV, the analysis of the fovea was done separately from the rest of the 60 regions as fovea represents proportionally the greatest part of V1. Preoperatively, there was no difference in foveal BOLD fMRI responses between anisometropic and myopic patients and controls. As shown in Figure 5d (IV), fovea mffMRI responses were found to be decreasing during follow-up. The only exception to this trend was control subject 1. Other participants excluding control subject 1 had not participated in fMRI experiments before this study. Control subject 1 had gone through fMRI experiments numerous times before. We can therefore conclude that this phenomenon was caused by habituation to the mffMRI examination.

Analysis of the fovea showed a decrease in the number of active voxels in anisometropic patients (Figure 5 e (IV)). A significantly smaller decrease in the number of active voxels was seen in myopic patients. In operated anisometropic eyes, there was a decrease of 65% in the number of active voxels of fovea at 12 months postoperatively compared to the preoperative state. In unoperated anisometropic eyes there was a decrease of 86%. In myopic patients and control subjects we found a decrease of 31% and 1% respectively in the number of active voxels of fovea at 12 months postoperatively.

When we studied the number of active voxels representing the innermost ring of the stimulus (Figure 1a (IV)), a similar phenomenon was encountered. In operated anisometropic eyes a decrease of 65% of active voxels in the innermost ring of the stimulus was found and in unoperated anisometropic eyes the corresponding
value was 85%. In myopic patients there was an increase of 28% in the number of active voxels at 12 months postoperatively compared to the preoperative state and in controls a decrease of 18%. 
Refractive surgery is nowadays widely used for the correction of refractive errors and there are actually long-term follow-up results available on myopic patients [Alio et al. 2008a, Alio et al. 2008b, Alio et al. 2008c, Alio et al. 2008d, Condon et al. 2007, Kymionis et al. 2007, O’Connor et al. 2006, Rajan et al. 2004, Zalentein et al. 2010, Zalentein et al. 2009]. Despite the increasing frequency of refractive surgery, there are only few studies on its use on anisometric or visually impaired adult patients.

It is generally thought that the visual system is malleable for only a certain period of time (known as the critical period), usually up to ten years of age. There are, however, publications supporting the idea that reversal of visual suppression may also occur after this critical period. Polat et al. have shown that by practising certain visual tasks, adult patients can improve their visual performance [Polat et al. 2004]. This is called perceptual learning. About 10% of anisometric or strabismic amblyopes show spontaneous improvement in the visual performance of the amblyopic eye if the visual acuity of the sound eye is reduced by injury or disease [Chua and Mitchell 2004, Klaeger-Manzanell et al. 1994, Rahi et al. 2002]. There are also reports showing that loss of the better-sighted eye has led to spontaneous recovery in visual function of adult amblyopic eyes [El Mallah et al. 2000, Kaarniranta and Kontkanen 2003, Wilson 1992]. Kaarniranta and Kontkanen reported a man with anisometric amblyopia whose VA in the amblyopic eye recovered to normal after loss of the dominant eye. Attempts had been made to treat this patient’s amblyopia in childhood but with little success [Kaarniranta and Kontkanen 2003]. Henriksson et al. studied patients with homonymous hemianopia in the chronic stage of stroke. They showed that intensive training of the blind hemifield can also induce cortical reorganization in the primary visual cortex [ Henriksson et al. 2007]. Maya Vetencourt et al. studied adult amblyopic rats. They found that chronic administration of fluoxetine, a widely used antidepressive, promoted the recovery of visual functions [Maya Vetencourt et al. 2008].

Earlier we have reported on an anisometric patient who recovered from migraine after refractive surgery [Holopainen et al. 2005]. At the age of 29 years, a neurologist diagnosed migraine with aura for this patient. By that time, this patient had suffered from headaches for over ten years. At the age of 33 years, the frequency of the migraine attacks was as many as 3-4 per week. The patient’s SEs were −4.25 D in the right eye and −9.5 D in the left eye. To correct anisometropia, both eyes of this patient were treated with LASIK. In March 2003 (seven months
after the surgery on the right eye and nine months after the surgery on the left eye) the difference in the refractive power of the eyes was only 0.125D. The patient’s migraines ceased by March 2003 when the final refraction was reached and the patient remained asymptomatic until the end of the follow-up (May 2004). This case suggested that severe anisometropia may induce functional changes in the visual pathways and these changes may induce migraine attacks.

Study I
In this study, 57 anisometropic patients and 174 myopic controls underwent refractive surgery. Mean preoperative BSCVA was found to be significantly higher for controls than for the non-amblyopic anisometropic patients (p=0.001). This finding suggested that anisometropic patients suffer from some degree of visual impairment. BSCVA improved among both anisometropic patients and myopic controls after refractive surgery but visual performance evolved differently in these two groups. In myopic controls, the improvement in BSCVA reached almost maximum at 3 months postoperatively. This concurred with earlier results of refractive surgery on myopic patients [Gartry et al. 1992, Stephenson et al. 1998]. For anisometropic patients the improvement in BSCVA was significantly slower than in myopic controls. In anisometropic patients, the improvement in BSCVA became statistically significant only 8-13 months postoperatively and appeared to continue to the end of the follow-up (24 months). These findings supported the idea of plastic changes in the visual cortex of adult anisometropic patients after refractive surgery, even beyond the conventionally defined critical period. However, the improvement of visual acuity in anisometropic pediatric patients after RS has been known for quite some time [Alio et al. 1998, Astle et al. 2002, Autrata and Rehurek 2004, Paysse et al. 2004, Paysse et al. 2006, Rashad 1999]. This improvement is probably due to loss of suppression.

In Study I, four of the anisometropic patients were mildly amblyopic, in other words, they had at least two Snellen lines difference between eyes in BSCVA. Yet, all these patients had BSCVA ≥ 20/40 even in the worse eye. One of the four mildly amblyopic anisometropic patients gained 3 lines at both 8-13 months and 25 months postoperatively compared to the preoperative situation. Two other mildly amblyopic anisometropic patients also gained two Snellen lines at 25 months postoperatively. This additional finding encouraged us to study the use of refractive surgery on visually impaired adult patients (Study III and IV).

Study II
In this study ten patients with a history of one or more RRD surgeries and subsequent refractive surgery were studied. Eight of these patients had anisometropia
of ≥ 2.5 D before refractive surgery. Most eyes become more myopic after scleral buckling surgery because the axial length of the eye increases [Beekhuis et al. 1993, Larsen and Syrdalen 1979, Malukiewicz-Wisniewska and Stafiej 1999, Smiddy et al. 1989]. This was also found in this study, as both the SE and degree of anisometropia increased after RRD surgery. The myopic shift in this study was found to be -2.4 D. This concurs with earlier results [Beekhuis et al. 1993, Burton et al. 1977, Larsen and Syrdalen 1979, Rubin 1975, Smiddy et al. 1989]. In Study II, a follow-up of a minimum of 40 months after refractive surgery was carried out (mean 67 months ±14). To the best of our knowledge, no other long-term follow-ups on such patients have been reported.

In this study, BSCVA was significantly better after refractive surgery than before scleral buckling surgery. These findings may suggest a reorganization of photoreceptor synapses, as has been previously shown in age-related macular degeneration [Sullivan et al. 2007]. On the other hand, a mean of 40 ±45 months after RRD surgery, mean BSCVA was -0.07 ±0.14 (Snellen 0.88±0.24), range -0.4 to 0.1 (Snellen 0.4 to 1.25) and this improvement in BSCVA was found to be statistically insignificant (p = 0.04). Likewise, BSCVAs before and after refractive surgery did not significantly differ. This may be because RRD impairs the visual performance. It is known that apoptosis causes photoreceptor cell degeneration at the early stage after traumatic retinal detachment [Chang et al. 1995].

A surprising result of this study was that only 5 of the 10 patients were within ±1.0 D of the attempted correction one month after refractive surgery, while at the last follow-up visit 6 were within ±1.0 D of the attempted correction. This result is poorer when compared to previously published reports on myopic patients undergoing RS [Hersh et al. 1997, Miyai et al. 2008, O'Doherty et al. 2006, Rajan et al. 2004]. This is likely to be due to difficulties in preoperative corneal measurements [Sakimoto et al. 2006]. In our study, three out of 4 LASIK patients were among those who were not within ±1.0 D. Farvardin et al. have published similar results [Farvardin et al. 2006]. They studied 14 eyes of seven patients. Each patient had undergone surgery for RRD and a following LASIK operation for both eyes. They found that 28% of the eyes with previous surgery for retinal detachment were within ±1 D of the attempted correction 1 year after LASIK whereas 85% of the fellow eyes without previous ocular surgery were within ±1 D of the attempted correction 1 year after LASIK. In light of our and Farvardin et al. results, it seems that it might be reasonable to favor PRK in patients with a history of scleral buckling surgery. However, this necessitates normal function of the corneal nerves [Tuunanen et al. 1997].

There are also concerns that LASIK patients with a history of RRD surgery are more prone to intraoperative complications. In our study, LASIK and PRK were performed by the same experienced surgeon and neither PRK nor LASIK patients suffered intraoperative or postoperative complications. During our follow-up, a
mean of 67 ± 14 months after refractive surgery, there were no new RRDs in our study group. We therefore conclude that in the long run PRK and LASIK are safe methods for the treatment of myopia in RRD patients after scleral buckling. This concurs with earlier studies showing that RS does not seem to put patients at higher risk of RRD [Ruiz-Moreno and Alio 2003].

**Study III**

In this study, adult visually impaired patients undergoing refractive surgery were studied. So far, studies on refractive surgery in visually impaired patients have mainly concentrated on children [Astle et al. 2002, Astle et al. 2007, Autrata and Rehurek 2004, Paysse et al. 2006, Tychsen et al. 2005]. These studies report improvement of visual acuity after RS.

Barequet et al., Lanza et al. and Roszkowska et al. have previously studied amblyopic adult patients after refractive surgery [Barequet et al. 2004, Lanza et al. 2005, Roszkowska et al. 2006]. None of these studies included a control group. Orucoglu et al. very recently published a report on adult patients with unilateral amblyopia who had been treated with LASIK [Orucoglu Orucov et al. 2010]. All their patients (n=30) had undergone bilateral refractive surgery. They found that the mean BSCVA improved both in amblyopic eyes and in the fellow nonamblyopic eyes. Five of those 30 amblyopic eyes gained 2 to 4 lines of BSCVA. The results of these studies are in agreement with our findings. Both in cohort 1 and 2, mean BSCVA among visually impaired patients improved nearly two Snellen lines 14-24 months postoperatively. As shown in Figure 3 (IIII), the difference in mean BSCVA between visually impaired patients and control subjects diminished during follow-up. In cohort 1, there was no statistically significant improvement in BSCVA in control subjects (p > 0.2). In cohort 2, statistically significant improvement in BSCVA was observed among control subjects. The minimum level of preoperative BSCVA for the refractive surgery to be effective was not found as the most amblyopic patients in our study gained Snellen lines during follow up. The results of Study III suggest that refractive surgery might also be used successfully in visually impaired adult patients. The improvement of BSCVA in visually impaired adult patients supports the idea of visual system’s plasticity continuing well beyond the conventional “critical period”.

**Study IV**

To the best of our knowledge this study was the first to address the impact of refractive surgery on the V1 in anisometropic non-amblyopic patients. The results of this study support the hypothesis that plastic changes take place in the primary
visual cortex of adult anisometropic patients after refractive surgery. A dramatic decrease in the number of active voxels of anisometropic patients’ fovea was found after RS. This was not found in myopic patients after RS or in controls. Changes similar to those found in the foveal region were found for all three groups when we studied the number of activated voxels in the innermost ring of the stimulus.

A likely explanation for this finding is that in anisometropic patients, a large network of neurons is activated for each visual stimulus. After surgery, the visual stimuli processing becomes more efficient as both eyes are equally involved and both eyes stimulate only a subgroup of neurons.

**General discussion**

The aim of this dissertation was to investigate the functional outcome of excimer laser refractive surgery in adult anisometropic and visually impaired patients and to examine changes in the primary visual cortex in anisometropic and isometropic myopic patients after RS.

We compared the results of the anisometropic patients and the visually impaired patients in this study. The analysis was done on those 96 visually impaired patients who had been followed up for a minimum of 5–7 months (n = 76) and on the anisometropic adult patients of Study I. In this analysis, BSCVA was measured before refractive surgery [76 (100%) visually impaired patients and 57 (100%) anisometropic patients] and 1 month (66% of the visually impaired patients and 65% of the anisometropic patients), 3 months (55% of the visually impaired patients and 79% of the anisometropic patients), 5–7 months (53% of the visually impaired patients and 54% of the anisometropic patients), 8–13 months (65% of the visually impaired patients and 43% of the anisometropic patients) and 14–24 months (55% of the visually impaired patients and 53% of the anisometropic patients) postoperatively. The comparison is shown in Figure 5 (III). Three months postoperatively, the visual performance was found to evolve similarly in these two groups. This finding suggests that the same sort of changes take place in these patient groups after refractive surgery.

The anisometropic patients and control subjects showed significant differences in the time needed to gain maximum improvement in BSCVA. The mean improvement of nearly two Snellen lines 14–24 months postoperatively in visually impaired adults indicated plasticity in the adult visual system. The dramatic decreases found in the number of activated voxels in the fovea of anisometropic patients after RS strengthens our hypothesis of plastic changes in the visual cortex of adult anisometropic patients after refractive surgery.
10 CONCLUSION

Excimer laser refractive surgery is nowadays widely used for the correction of refractive error. Earlier studies have concentrated on the use of refractive surgery on isometropic myopic patients.

The aim of this dissertation was to study the use of refractive surgery on adult anisometropic and visually impaired patients and to examine changes in the primary visual cortex in anisometropic and isometropic myopic patients after refractive surgery. No treatment is currently available for adults with visual impairment.

Our results suggest that plasticity also exists in adult brains. The results revealed that refractive surgery may be successfully used for the treatment of anisometropic adults with both congenital and iatrogenic anisometropia and for visually impaired adults.
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