The Role of Extraocular Muscle Afferent Signals in Oculomotor Control and Spatial Localisation

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SUMMARY

The extraocular muscles are richly endowed with sensory receptors. However, the precise role of afferent signals derived from these proprioceptors in visuomotor control is not fully understood, and has been the subject of considerable debate for more than a century. This has been investigated in more detail in these studies.

Part 1 of this thesis provides a review of previously published work concerning both the existence and the function of extraocular muscle afferent signals in oculomotor control and spatial localisation.

Part 2 of this thesis investigates oculomotor control. This was done by using an infrared corneal reflection device to record eye movements under different experimental conditions. Initially, an assessment of the reproducibility of this technique was performed in a population of normal adults. This confirmed that it was an accurate method for the repeated measurement of eye movements. The effect of experimentally impeding the movement of one eye, using a suction contact lens, on both saccades and smooth pursuit eye movements of the contralateral eye was then investigated. This technique is thought to modify non-visual afferent signals from the impeded eye, most likely to be derived from extraocular muscle proprioceptors. The results showed that for saccadic eye movements, the amplitude and peak velocity of the contralateral eye was reduced when one eye was impeded. However, the main sequence parameters remained unchanged. For smooth pursuit eye movements, the initial acceleration and velocity of the contralateral eye were reduced when one eye was impeded. These findings indicate that extraocular muscle afferent signals can under certain circumstances, influence the oculomotor control of both the saccadic and smooth pursuit systems.

Part 3 of this thesis investigates spatial localisation. This was appraised by asking subjects to point at targets appearing on a computer touchscreen without being able to see the pointing hand. Initially an assessment of the reproducibility of this technique was performed in a population of normal children and adults to ensure that it was an accurate method for this purpose. Spatial localisation was then assessed in a group of 60 children with one particular type of strabismus, namely fully accommodative esotropia. A comparison was made of their pointing responses when their eyes are aligned

(when wearing glasses) and when there is a manifest squint (not wearing glasses). The results showed that their perception of the central target position shifted in the direction of the non-squinting eye when their deviations are manifest. These findings are thought to be due to an alteration in extraretinal eye position information, derived in part, from extraocular muscle afferent signals, which helps to specify visual direction. A further study investigated the pointing responses of two groups of patients undergoing different forms of surgery for primary rhegmatogenous retinal detachment. The results showed that those patients undergoing conventional external scleral buckling procedures, and to a lesser extent those undergoing vitrectomy procedures, demonstrated significant changes in spatial localisation on the first post-operative day when viewing central and eccentric targets with their fellow unoperated eye. These changes had returned to normal by the subsequent follow-up assessment approximately 10 days later. Again these findings are believed to be due to alterations in the extraretinal eye position signal, the source of which is likely to be modified extraocular muscle proprioception derived from the operated eye as a consequence of the surgical procedure.

In conclusion, these studies have shown that under certain circumstances, an intervention affecting one eye, be it experimental or surgical, can influence both the oculomotor control and spatial localisation of the contralateral eye. This is the result of modified non-visual afferent information, most likely originating from within extraocular muscle proprioceptors. Not only do these findings contribute to our understanding of the basic mechanisms involved in visuomotor control, they may also have clinical implications by highlighting the potential effect of surgery involving the extraocular muscles, most notably strabismus procedures, on aspects of visual function that are often overlooked.

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PREFACE

It has been known for a considerable period of time that the extraocular muscles are richly endowed with sensory proprioceptors, although their precise function is poorly understood. This became of interest to myself when I realised that strabismus surgery almost inevitably damages the very areas of the muscles containing these receptors, and yet little is known about the effect this has (if any) on patients' eye movements or spatial perception. Unfortunately these issues are not addressed in standard strabismus texts. In addition, several key articles in the scientific literature have dismissed the role of extraocular muscle afferent signals in human visuomotor control. I found it difficult to accept that a complex system such as that controlling the oculomotor apparatus would not utilise all available information to meet its exacting and demanding needs. This led to the studies of the role of extraocular muscle afferent signals that are presented in this thesis.

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PART 1 : INTRODUCTION

CHAPTER 1 :
EXTRAOCULAR MUSCLE AFFERENT SIGNALS

1.1 INTRODUCTION

The co-ordinated movement of both eyes is essential for effective vision and visually guided behaviour [67]. For this to occur accurately we require to 'know' the direction in which our eyes are pointing. If the eyes were fixed within the orbits then retinal (i.e. visual) information by itself would be sufficient to tell us where we are looking. However, the eyes are free to move and under these circumstances additional, extraretinal (i.e. non-visual) information is required, which relates to the position of the eyes within the orbit thereby allowing the direction of gaze to be determined.

There are two broad hypotheses that seek to explain the source of this extraretinal information, and whilst not mutually exclusive, they have commonly been presented as alternatives. The 'inflow' hypothesis, holds that afferent signals from the effector muscles in the oculomotor system, the extraocular muscles, provide the necessary information about the positions of the eyes within the orbits and about movement of the eyes. This view can be attributed to Sherrington [105], although it fell out of favour particularly in the 1960s, when the role of muscle receptors in general came to be doubted (see Matthews [78] for review). The 'outflow' hypothesis, attributed to Helmholtz [57], holds that central monitoring of a copy of the motor command sent to the extraocular muscles (also known as efference copy [58] or corollary discharge [109]) provides the necessary extraretinal information to determine eye position. While in reality both afferent and efference copy signals are probably involved, the relative contribution of each has been the subject of considerable debate for over a century. This chapter will outline the anatomical and physiological evidence supporting the 'inflow' hypothesis.

1.2 EVIDENCE FOR THE PRESENCE OF SENSORY 'INFLOW'

1.2.1 Innervation

Whilst the motor innervation of the extraocular muscles is well established, their sensory innervation has generated a great deal of controversy [8, 108]. Two types of sensory receptor have been identified within the extraocular muscles, namely muscle spindles [74, 101] and myotendinous cylinders (palisade endings)[96].

Muscle spindles are located in the proximal and distal thirds of human extraocular muscles [26, 80]. Their structure differs from that of other species and also from spindles of other skeletal muscle [101]. They consist of thin intrafusal fibres within a connective tissue capsule and lie in parallel with the extrafusal fibres. Two types of sensory ending are normally present in muscle spindles, namely group I afferent fibres which arise from primary (annulospiral) endings, and group II fibres which arise from secondary ("flower spray") endings. While spindle sensitivity is usually modulated by the gamma motor innervation, little is know about the role of gamma innervation in the extraocular muscles. Although extraocular muscle spindles are found in infant and elderly subjects at a density similar to that of spindles in hand and neck muscles (which suggests a role in fine motor control [13, 74]) their proprioceptive capacity has been questioned [73, 103]. Ludvigh [73] believed that "muscle spindles give rise to little, if any, acceptable information concerning the position of the eyes" while Ruskell [103] found structural features within muscle spindles such as the presence of anomalous fibres within the connective tissue capsule, which he argued could jeopardise their proprioceptive function. However, structural considerations alone cannot settle the issue and are no replacement for functional observations (which are discussed in later chapters).

The other main sensory receptors of skeletal muscle, Golgi tendon organs, are not present in human extraocular muscles [96, 107] although they have been identified in other species such as the sheep [102] and the monkey [100].

Myotendinous cylinders (palisade endings) appear to be a class of muscle

receptor unique to the extraocular muscles and are found within the distal myotendinous junction of the extraocular muscles both in man and monkeys [99, 96, 75]. They consist of networks of fine neural filaments closely associated with the end of a single extrafusal muscle fibre and are surrounded by a thin capsule [5]. Greater numbers of myotendinous cylinders are found within the horizontal compared to the vertical rectus or oblique muscles [99]. Given their intimate association with extrafusal fibres, a specialist role in monitoring extraocular muscles function has been suggested [96], in particular a response to active contraction of their associated muscle fibres. However, as no one has yet succeeded in recording from palisade afferent fibres, the precise information they transduce is not known. Nevertheless, in view of their location at the distal myotendinous junction, the very area at which the majority of strabismus procedures are performed, it is tempting to speculate that disrupting these receptors during surgery could lead to alterations in oculomotor control and affect the outcome of surgery.

1.2.2 Peripheral Pathways and Central Connections

The primary afferent pathway from the extraocular muscles to central processing structures has also generated a degree of controversy. Animal studies have shown that afferent fibres travel for a variable distance with the motor cranial nerves (III, IV and VI) before crossing to travel in the ophthalmic branch of the trigeminal nerve [28, 11, 51]. The balance of the evidence indicates that the vast majority if not all the primary afferent cell bodies are located within the trigeminal ganglion in various species, including monkeys [90], cats [91], birds [56] and rabbits [59] . Primary afferent fibres terminate in the ipsilateral spinal trigeminal nucleus in the cat [21] and in the monkey, in which there is also a secondary projection to the cuneate nucleus [90, 21]. The effects of the stimulation of extraocular muscle afferent signals have been detected in a large number of visual and oculomotor structures in a variety of species, and include the cerebellum [10], the vestibular nuclei [22], the abducens nucleus [37] and the superior colliculus [1].

The balance of the evidence is, therefore, that extraocular muscle afferent signals are available to oculomotor and visual control centres, and have the potential to influence the processing of information within these centres, thereby modifying visuomotor behaviour.

1.3 FUNCTION OF EXTRAOCULAR MUSCLE AFFERENT SIGNALS

The evidence not only for the presence of sensory receptors within the extraocular muscles, but also for their capability of conveying afferent signals to all of the important structures involved in visual and oculomotor control has been outlined above. The next issue that warrants consideration is the exact role of extraocular muscle afferent signals. There is increasing evidence from experiments in both animals and humans that extraocular muscles afferent signals are important in three broad areas of visuomotor control. Firstly, oculomotor control, secondly, in spatial localisation (by providing afferent information about the position of the eye within the orbit, which in turn helps to determine visual direction [111, 18]) and thirdly in the development and maintenance of normal binocular visual function. The role of extraocular muscles afferent signals in oculomotor control and spatial localisation will be considered in Chapters 2 and 3 respectively. The importance of extraocular muscles proprioception in binocular function was demonstrated by studies showing that deafferentation results in impaired development of both orientation selectivity within the visual cortex [19] and depth perception [43]. A more detailed discussion of this is provided by Steinbach [111] and Buisseret [18].

CHAPTER 2 :
THE ROLE OF EXTRAOCULAR MUSCLE AFFERENT SIGNALS IN OCULOMOTOR CONTROL

2.1 INTRODUCTION

Eye movements are mediated by a complex hierarchy of neuronal systems. While the pathway consists of the motor nuclei and associated structures in the brainstem, oculomotor behaviour is shaped by the cerebellum, the superior colliculus, the basal ganglia, and the cortical eye fields [67]. The two types of eye movement of relevance to these studies are saccades and smooth pursuit. The neural pathways controlling these eye movements systems will therefore be discussed in more detail.

Saccades are rapid eye movements designed to bring visual targets of interest onto the fovea [67]. Their characteristic feature is the pulse-step: the pulse representing an increase in innervation required to move the eye to its new position; the step representing the new level of innervation that is required to maintain the new gaze position. Saccadic eye movements are produced by the common brainstem generator, which is made up of the pre-motor nuclei of the paramedian pontine reticular formation for horizontal saccades, and the rostral interstitial nucleus of the medial longitudinal fasiculus for vertical and oblique saccades. From within these pre-motor structures excitatory and inhibitory burst neurons determine the activity of agonist and antagonist extraocular muscles respectively. In turn, these burst neurons are under the control of omnipause neurons, which tonically inhibit their activity until a saccade is required. The saccade generating machinery within the brainstem is controlled and influenced by several neuroanatomic structures acting in concert to produce eye movements of the desired speed and direction. These include specific sites within the cerebral hemispheres, the superior colliculus, the basal ganglia and the cerebellum, all of which ultimately project either directly or indirectly to the brainstem reticular formation. Descending pathways from the frontal cortex areas such as the frontal eye fields, the dorsolateral prefrontal cortex and the supplementary eye fields via the superior colliculus are believed to play a role in

the programming of volitional saccades. Pathways from the parietal eye fields contribute more to reflex saccades, enabling the oculomotor system to shift the direction of gaze to newly appearing targets. The superior colliculus is of particular importance for such visually driven reflex saccades. In contrast the basal ganglia inhibits unnecessary reflex saccades thereby helping fixation on targets of interest, as well as contributing to the initiation of more voluntary saccades. The cerebellum plays a pivotal role not so much in the generation and programming of saccades but rather in calibrating and co-ordinating the accuracy of saccadic eye movements. These oculomotor centres form a complex network of neural pathways designed to optimise saccade behaviour.

Smooth pursuit eye movements are designed to allow clear vision of a moving target by stabilising the image on the retina. Target motion itself is the stimulus for the pursuit response, with information about its speed and direction carried from the retina via the geniculostriate pathways to the secondary visual areas, namely the homologue of the middle temporal and medial superior temporal areas, where motion processing occurs. From here there are projections to the frontal eye field, which together with the supplementary eye field is thought to be involved in the programming of the predictive components of pursuit eye movements. The posterior parietal cortex also receives input from the middle temporal and medial superior temporal areas, and is believed to have a role in determining the target to be followed. There are independent descending pathways from the secondary visual areas and the frontal eye fields, which converge on the dorsolateral pontine nuclei. This area may be important in integrating eye movement signals with visual information. Projections from the nucleus of the optic tract also reach the pontine nuclei and may play a role in pursuit initiation. The relevant projections from the pontine nuclei are to the contralateral cerebellum, which plays a crucial part in the generation of smooth pursuit movements, with the dorsal vermis linked to the initiation of pursuit, while the flocculus and paraflocculus contribute to the maintenance of the pursuit response.There are projections from these cerebellar areas to the ipsilateral vestibular nuclei, which in turn project to the contralateral oculomotor nuclei within the brainstem. Constant monitoring of this complex

system via visual input is designed to ensure accurate pursuit eye movements.

As outlined in chapter 1, vision combined with efference copy are the predominant sources of information utilised to co-ordinate the movement of the eyes, with a role for extraocular muscles afferent feedback in the oculomotor system usually discounted, particularly as the extraocular muscles operate under conditions of a fixed mechanical load [16, 25]. This chapter will discuss the evidence supporting extraocular muscle proprioception as a contributory factor in oculomotor control. This can be considered in two broad areas; firstly evidence derived from animal studies, and secondly evidence derived from studies in human subjects.

2.2 EVIDENCE DERIVED FROM ANIMAL STUDIES

Animal studies have shown that proprioceptive input influences both gaze holding and gaze shifting systems. For example, extraocular muscle deafferentation by sectioning the ophthalmic branch of the trigeminal nerve affects fixation stability in cats [44] and causes deviation of the eye position in lambs[89]. Section of the III, IV and VI cranial nerves of one eye in the cat, disrupting afferent feedback, alters the fixation stability of the contralateral eye in the dark [76]. O'Keefe and Berkley [85] demonstrated that in anaesthetised cats, retrobulbar injection of a paralytic drug reduced eye movements in both the ipsilateral treated eye *and* the contralateral untreated eye. They concluded that afferent signals from extraocular muscles mediated this effect possibly by influencing the central motor command signal. Further studies have also shown that proprioception contributes to the maintenance of ocular alignment during fixation in monkeys [71].

In addition to the stability of the eyes within the orbits, proprioception also modifies eye movements. For example, the conjugacy of saccadic eye movements in monkeys is impaired by deafferentation [71]. There is considerable evidence that extraocular muscle afferent signals modify the processing of vestibular information and in so doing alter eye movements

generated by the vestibular system [64]. Removal of the proprioceptive input from extraocular muscles by sectioning the ophthalmic branch of the trigeminal nerve disrupts the slow phase and reduces the gain of the vestibulo-ocular reflex (VOR) in rabbits [59, 62]. Manipulating extraocular muscle afferent signals by imposing movements on one eye modifies the output of the VOR of the contralateral eye in pigeons and indicates that such signals may be important in the moment to moment control of the VOR [38, 63]. These effects have been demonstrated not only in reduced experimental preparations, but also in the alert behaving animal [40]. In addition, Kimura et al [62] have shown that interrupting the extraocular muscle afferent pathway in rabbits modifies the gain and velocity of optokinetic nystagmus.

The timescale over which proprioceptive feedback might act upon the oculomotor control system in animals is the subject of some debate. While it has been argued that it functions over the long term to bring about adaptive parametric adjustment of eye movements [71], much of the physiological evidence discussed above is suggestive of a more immediate effect [38].

2.3 EVIDENCE DERIVED FROM HUMAN STUDIES

Two main experimental methods have been described for studying the role of extraocular muscle afferent signals in human studies: vibration of the muscle tendon and passively moving the whole eye.

Vibrating a muscle tendon is a recognised way of stimulating muscle spindles in particular [53] and generates an afferent signal that is interpreted by the central nervous system as stretching of the muscle. This technique has been used specifically to induce extraocular muscle afferent signals [116]. The second method involves passively moving an eye using a scleral contact lens held in place with gentle suction . This technique probably has the advantage of modifying the proprioceptive input from all the extraocular muscles simultaneously [48], although how closely the resultant afferent signal resembles that produced by voluntary contraction is unclear. Using these approaches, observations have been made in both normal subjects and patients

that suggest a role for extraocular muscle afferent signals in the control of eye movements.

Gauthier et al [50, 49] demonstrated that after a period of passive deviation of one eye a change in phoria is observed which corresponds to the direction of the original deviation. For example, deviating the right eye temporally resulted in an increased exophoria, as measured by the Lancaster red-green dissociating test. This effect, which persisted for several minutes after the suction contact lens was removed, was quickly eliminated by binocular viewing. The authors suggested that the change in ocular alignment was due to an interaction between extraocular muscle afferent signals and central control mechanisms. Lennerstrand et al [68] have shown, using single extraocular muscles vibration, that both the vertical and horizontal position of the non-stimulated eye could be modified depending on the extraocular muscles stimulated. For example, vibrating the inferior rectus muscle of one eye in normal subjects induced an upward movement of both eyes, while vibration of the lateral rectus muscle induced an abduction movement of the contralateral eye. The exact mechanism by which this occurs is unclear. However, direct interactions between afferent signals from individual extraocular muscles and the motor nuclei of synergistic and antagonist muscles are highly unlikely given the earlier discussion on the route of the afferent pathway. Interestingly, the response of exotropic subjects to vibration of the lateral rectus was opposite to that seen in normal subjects; an adduction movement was noted in the contralateral eye. This suggests an altered pattern of central processing of extraocular muscle afferent signals in these subjects.

Both saccades and smooth pursuit can also be modified by extraocular muscle proprioception. Saccadic eye movements, because of their short durations and high velocities, are usually considered to be ballistic i.e. not under feedback control. While visual feedback is certainly too slow for the control of individual saccades, extraocular muscle afferent signals might theoretically be involved. Using the single extraocular muscle vibration technique, the programming of memory guided saccades was shown to be influenced by altering extraocular

muscle proprioception [3]. The adaptive response of the smooth pursuit system to changes in target velocity has also been modified using proprioceptive feedback [114].

It might be argued that all of these studies involve non-physiological manipulations of extraocular muscle afferent feedback, thereby inducing aberrant interactions in the oculomotor control circuitry, which in turn leads to altered or degraded oculomotor behaviour. However, allied to the anatomical and structural findings discussed above, these results clearly indicate that extraocular muscle afferent signals can influence the control of eye movements.

This viewpoint is further strengthened by observations in patients, which suggest that extraocular muscle afferent signals may be important in the aetiology of certain oculomotor disorders. For example, studies in subjects with congenital strabismus have shown alterations in the morphology of extraocular muscle proprioceptors, such as smaller size and a disorganised structure [30]. However, it is not possible to be sure whether these changes are the cause or the consequence of the strabismus and further studies are needed to confirm these findings. Mitsui [82] has argued that extraocular muscle afferent signals are involved in the pathogenesis of both exotropia and esotropia. It was found that in exotropic patients, slight passive adduction of the non-deviated eye using forceps causes the deviating eye to straighten. This observation was termed the "magician's forceps phenomenon". The underlying cause of the exodeviation was believed to be abnormal proprioceptive input from the non-deviated eye, which caused excessive contraction of the lateral rectus of the contralateral, deviating eye. When the non-deviating eye was passively adducted the resultant stretch of the lateral rectus muscle modified the afferent input to the oculomotor centres which in turn influenced the position of the contralateral eye. Analogous observations could only be made in esotropic patients using electromyography. Although the interpretation of these observations has been questioned [18] they do suggest that an imbalance in extraocular muscle afferent information may affect oculomotor control.

Interestingly, modified extraocular muscle proprioception has been proposed as

a factor in the aetiology and treatment of congenital nystagmus. Optican [88] suggested that erroneous afferent feedback regarding eye velocity is important in the development of this form of nystagmus. In addition, Dell'Osso et al [32] have recently reported damping of congenital nystagmus following staged tenotomy of all the extraocular muscles in an animal model. They suggest that this effect is due to an alteration in proprioceptive feedback from the extraocular muscle as a result of the tenotomy procedure. Whilst acknowledging that such a procedure risks causing anterior segment ischaemia in humans, they argue that a modified procedure, consisting of bilateral medial rectus recession combined with bilateral lateral rectus tenotomy, may provide a potential surgical therapy for this condition.

The balance of the evidence is, therefore, that extraocular muscle afferent signals are not only available to oculomotor and visual control structures, but that they influence the processing of information in these structures, thereby modifying visuomotor behaviour.

However, two key pieces of experimental evidence are often quoted to counter this proposition. The first comes from Keller and Robinson [60], who reported that in the monkey, there is no monosynaptic stretch reflex in the oculomotor system. While recording from single units in the abducens nucleus, they found no alteration in firing rate when an external force moved the ipsilateral eye, or when a self-generated movement was impeded. However, it should be remembered that the failure to demonstrate the existence of a direct ipsilateral feedback pathway onto the motoneurons does not mean that an alternative pathway for afferent signals is not present. The second important piece of evidence was provided by Guthrie et al [54] who noted that monkeys could still make accurate saccades in the absence of extraocular muscle afferent signals. However, once again showing that saccades can be executed accurately without afferent feedback, is not equivalent to demonstrating that afferent feedback plays no role when it is available. It may be that when the afferent pathway is damaged or degraded, or indeed manipulated, there is sufficient redundancy and flexibility to ensure that performance recovers. All of this still leaves open the issue of the precise time course of modification. Ludvigh [72] suggested that

the mode of action was consistent with a long-term adaptive effect in which afferent feedback induces modifications in efferent motor commands. As already noted however, a number of key experimental results are actually more consistent with action on a far shorter timescale. This might be evidence for a fast adaptive process unique to the oculomotor system or even on-line control of individual oculomotor or visuomotor acts. The increasing awareness of extraocular muscle proprioception is reflected in a recently described theoretical model in which information derived from efference copy and afferent feedback are integrated, with both playing a fundamental role in oculomotor control[83].

2.4 DISCUSSION

Knowledge of the position of the eyes within the orbits is a prerequisite for co-ordinated eye movements, gaze shifts and accurate visuomotor behaviour. Although vision itself, combined with central monitoring of outflowing neural discharge to the extraocular muscles, provides much of the required information, there is now considerable experimental and clinical evidence that inflowing proprioceptive signals from the extraocular muscle make a vital contribution. Animal and human studies have demonstrated that removing or manipulating extraocular muscle afferent input not only affects static eye position but can also modify smooth pursuit, saccades and the vestibulo-ocular reflex. A greater understanding of the role of proprioception in oculomotor control would be beneficial not only from a theoretical viewpoint but also in everyday clinical practice as strabismus surgery, a commonly performed procedure, involves manipulating areas of the extraocular muscles richly endowed with proprioceptors. Little is known as to what effect, if any, different methods of handling these tissues might have on surgical success.

CHAPTER 3 :
THE ROLE OF EXTRAOCULAR MUSCLE AFFERENT SIGNALS IN SPATIAL LOCALISATION

3.1 INTRODUCTION

The ability to locate targets in surrounding visual space (egocentric or spatial localisation) is an essential part of normal visual function. It is of practical importance in everyday life in a wide range of ways, from simply reaching for an object to more complex tasks such as driving a car. For this to occur accurately the brain relies upon retinal and extraretinal information to specify visual direction. However, as discussed in chapter 1, the contribution of extraocular muscle afferent input to the eye position signal that is utilised in spatial localisation is disputed. This chapter considers this subject in greater detail.

The evidence implicating a role for extraocular muscle proprioception in spatial localisation in humans is derived from two main sources: firstly observations in patients in whom the afferent input has been disrupted either pathologically or surgically and secondly experimental studies in normal subjects in whom the afferent signal has been manipulated.

3.2 EVIDENCE DERIVED FROM PATIENT OBSERVATIONS

Steinbach [110] studied one patient in whom the ophthalmic division of the trigeminal nerve was surgically sectioned as treatment for trigeminal neuralgia, a procedure which is thought to abolish afferent input from the ipsilateral extraocular muscles. When this patient's ability to point to targets in surrounding visual space was tested without his being able to see the pointing hand, greater inaccuracies were recorded when the de-afferented eye was viewing. Any interpretation of these results has to be cautious as they were obtained from a single subject but they do suggest that loss of proprioceptive eye position information causes an alteration in the centrally registered position of the eye, which in turn results in errors in spatial localisation. Ventre-Dominey et al [117] studied patients with trigeminal neuralgia who

subsequently underwent unilateral thermocoagulation of the trigeminal nerve. Following surgery these patients were found to have deficits in spatial localisation, which were not present pre-operatively. Again this was thought to be a consequence of the surgical procedure causing a change in the proprioceptive eye position signal which in turn produced inaccuracies locating targets in surrounding visual space. The authors concluded that a balanced proprioceptive input is required for accurate egocentric localisation. Campos et al [24] noted that 5 out of 6 patients with active herpes zoster ophthalmicus demonstrated errors in open-loop pointing tasks (in which subjects point to a target without being able to view their pointing hand) when using the affected eye. This was attributed to temporary disturbance of the proprioceptive signal from the extraocular muscles as a result of viral infection of the ophthalmic branch of the trigeminal nerve. These pointing errors disappeared with resolution of the disease. It is surprising, however, that errors were not found when the unaffected eye was tested, particularly as afferent feedback from both eyes is thought to contribute to the extraretinal eye position signal utilised in spatial localisation [116].

Campos et al [23] presented further evidence for the role of proprioception in spatial perception after finding localising errors when the operated eye was viewing, in 11 patients who had undergone encircling procedures for retinal detachment. Presumably the presence of the encircling band in the operated eye affects the afferent information originating from the extraocular muscles, resulting in an erroneous eye position signal. This in turn may affect the perception of the location of a target in surrounding visual space.

Lewis & Zee [70] studied a patient with congenital trigeminal-oculomotor synkinesis, in which the left medial rectus muscle was innervated by the trigeminal nerve resulting in an adduction movement of the left eye when the left lateral pterygoid muscle contracted. This enabled them to deviate the left eye, thereby stimulating the extraocular muscle afferent input, without modifying the normal oculomotor efferent command, and assess what effect this had on open-loop pointing responses. They subsequently found significant pointing errors when the right eye was viewing targets monocularly and

concluded that proprioceptive afference about eye position from the affected left eye was used in the process of spatial localisation of the normal right eye.

Observations in strabismic patients have also added weight to the argument that proprioception has a role in visual localisation. It is well documented that such patients produce errors when asked to perform tasks involving spatial perception [77] and although the aetiology of these errors is complex [45] abnormal extraocular muscle proprioception may be a contributory factor. For example, Steinbach and Smith [113] found significant differences in pointing responses following surgery when comparing patients being operated on for the first time, with patients who had previously undergone surgery to the same eye muscles. The newly operated patients were able to locate targets with accuracy, indicating that they had access to information about the altered position of the eye. As the eyes were covered post-operatively until testing took place the authors concluded that this new information could only be of proprioceptive origin. In contrast, the previously operated patients showed greater pointing errors suggesting that they lacked afferent information about the altered eye position. The authors speculated that prior surgery had damaged proprioceptors located within the muscle tendon resulting in disrupted inflowing afferent signals about the new position of the eye. However, in a similar study, Bock and Kommerell [15] disputed these findings and believed that the changes observed in visual localisation following strabismus surgery were compatible with efference copy. However, in their patients surgery was performed under local anaesthesia rather than general anaesthesia, which might explain their findings (see Steinbach [111]).

Spatial localisation is not only affected by strabismus surgery *per se,* but also by the type of surgical procedure performed. For example Steinbach et al [112] tested esotropic patients who underwent either a recession procedure or marginal myotomy. They found that patients undergoing muscle recessions had fewer pointing errors post-operatively when compared with those patients in whom a marginal myotomy was performed. The authors concluded that the proprioceptive input that signalled the new eye position was impaired to a greater extent by the myotomy procedure than by the recession. This was

thought to be due to disruption of the palisade endings, which are preferentially located at the musculotendinous junction, the site affected by the myotomy procedure. In contrast, the recession operation involved manipulating the muscle tendon only, which is not well endowed with palisade endings. Dengis et al [34] showed that these changes in spatial localisation observed following strabismus surgery were the result of an alteration or recalibration in the perceived position of the eye within the orbit rather than a shift in the egocentre location. Unfortunately, however, some of the above studies involving strabismus patients include subjects with dissimilar types of strabismus, who in addition have undergone different numbers of surgical procedures. This results in relatively small numbers of patients per group, which could affect any firm conclusions being drawn from such studies.

Injection of botulinum toxin into the extraocular muscles can be used as an alternative to surgery in the treatment of strabismus [104]. Dengis et al [33] investigated the effect of this treatment on proprioceptive feedback by assessing open-loop pointing responses in strabismus patients before and after botulinum injection. They found no change in spatial localisation immediately following the injection, when viewing with the injected eye, but significant changes were observed several days later, which is not surprising given the time course over which botulinum acts. They concluded that botulinum toxin alters proprioceptive feedback from palisade endings located within the extraocular muscle EOM but only over the long term.

3.3 EVIDENCE DERIVED FROM EXPERIMENTAL STUDIES

As discussed in Chapter 2 it has been suggested that afferent signals from extraocular muscle proprioceptors can be manipulated experimentally in normal subjects by either vibrating the muscle [97] or by passively deviating one eye [48]. Using these techniques the role of inflowing eye position information in spatial localisation has been investigated further.

3.3.1 Muscle Vibration :

Vibration of the extraocular muscle has been shown to induce an illusion of target movement [97, 98, 116, 115]. These studies demonstrated that when subjects fixated a luminous object in total darkness, vibration of either the inferior or horizontal rectus muscle of one eye resulted in an apparent movement of the object. Velay et al [116] have also demonstrated that vibrating the inferior rectus muscle results in pointing errors in spatial localisation tasks, and that these are greatest when the dominant eye is vibrated. In addition significant errors are noted when the vibrated eye is occluded and the contralateral eye used for viewing. These responses could only be obtained in darkness and were not detectable when a structured visual background was used. The authors concluded that vibration activates proprioceptors to signal stretching of the vibrated muscle and that this is interpreted by the visuomotor system as an erroneous change in eye position which in turn results in mislocation of targets in surrounding visual space. This suggests that the proprioceptive eye position signal derived from both eyes is used to specify a common visual direction, and may only come into play when moving in conditions of darkness. Han and Lennerstrand [55] have recently reported differences in visual localisation between normal and strabismic subjects following vibration of the eye muscles. For example, vibrating the lateral rectus muscle of the non-viewing eye in both groups of subjects caused a perceived shift in the position of a target in opposite directions. They suggest that this difference could be related to the poor binocular function of the strabismic group, which in turn might affect the integration of proprioceptive information from each eye.

Vibration of the neck muscles has also been shown to affect spatial localisation in normal subjects [12, 98], which suggests that proprioceptive feedback from the neck muscles also contributes to the extraretinal signal that is required to determine the direction in which the eyes are pointing, presumably by specifying head position with respect to the body. Interestingly, it has recently been shown that the effect of proprioceptive activation of neck muscles on spatial localisation differs in patients with constant strabismus when compared with normal subjects [55]. Again this is thought to relate to the degree of binocular

function in each of these two groups.

3.3.2 Passive Eye Movement :

Gauthier et al [48] showed that passively deviating one eye in normal subjects caused errors in locating objects in the surrounding visual space when viewing with the contralateral eye. These errors were in the same direction as the passive eye movement. They concluded that as the outflowing efferent signals to the extraocular muscle were similar in both the control and experimental subjects, the difference in spatial localisation resulted from altered proprioceptive input from the deviated eye. Using the same technique Gauthier et al [50] have also reported that these errors in spatial localisation persist even after the suction contact lens is removed and the eye is no longer deviated. Moreover, these errors were present irrespective of which eye was used for viewing. Their findings were thought to be due to a small degree of ocular misalignment, which persisted for a short period of time after the suction lens had been removed. This in turn altered the central registration of the position of both eyes resulting in impaired spatial localisation and demonstrated that extraocular muscle proprioception is involved in the long term control of eye alignment.

3.4 DISCUSSION

There is increasing evidence that inflowing proprioceptive information originating from the extraocular muscle can play a part in spatial localisation by contributing to the extraretinal eye position signal. Although outflow is likely to be the main source of this signal [25] the potential importance of inflow should not be discounted, particularly in the context of darkness. Spatial localisation is not only of theoretical interest, but may be of relevance from a clinical viewpoint as the author has noted that some patients with ocular motility disorders complain that objects are not always where they appear to be in the visual world. This observation has important implications for tasks in everyday life such as driving and may be related to alterations in extraocular muscle proprioception. In addition, not only do strabismus patients have difficulty with

spatial localisation [45, 77] but corrective surgery can affect this to varying degrees depending not only on the type but also on the number of operations performed [113, 112]. This could potentially influence the choice of surgical procedure carried out in such patients in the future.

Whilst outflow is still likely to be the predominant source of information determining visual direction, and much still needs to be done to establish the exact role of extraocular muscle proprioception in visuomotor control, it seems reasonable, as suggested by Matthews [78], to consider them as complementary rather than mutually exclusive.

CHAPTER 4 :
AIMS OF THESIS

4.1 Aims of thesis

The aims of this thesis are:

1. To investigate the role of extraocular muscle afferent signals in oculomotor control in normal adult subjects.
2. To investigate the role of extraocular muscle afferent signals is spatial localisation in patients with strabismus, and in patients undergoing surgical procedures which involve manipulating the extraocular muscles.

4.2 Research questions

The research questions to be addressed by this study are:

1. *What effect does manipulating extraocular muscle afferent signals from one eye have on saccadic eye movements of the contralateral eye, in normal adult subjects?*

   A suction scleral contact lens is used to impede the movements of the right eye while subjects execute visually guided saccades to briefly presented targets. This technique is thought to modify afferent feedback from the extraocular muscles of the impeded eye [48]. Movements of the left eye are measured using infrared oculography. Comparisons of the saccade amplitude, peak velocity and duration before, whilst and after the right eye is impeded are then made.

2. *What effect does manipulating extraocular muscle afferent signals from one eye have on smooth pursuit eye movements of the contralateral eye, in normal adult subjects?*

   A suction scleral contact lens is used to impede the movements of the right eye while subjects execute smooth pursuit eye movements. Movements of the left eye are measured using infrared oculography. Comparisons of the initial

acceleration, velocity and latency of the smooth pursuit response before, whilst and after the right eye is impeded are then made.

3. *Is spatial localisation in children with one particular type of strabismus (fully accommodative esotropia) affected by refractive correction?*
   Children with fully accommodative esotropia are asked to point to targets appearing on a computer touchscreen, without being able to see their pointing hand. Comparisons of the horizontal pointing errors recorded whilst wearing glasses (i.e. no manifest deviation) and not wearing glasses (i.e. manifest deviation) are then made.

4. *Is spatial localisation in patients with retinal detachments affected by surgical repair (which involves manipulating the extraocular muscles), and is it influenced by the type of procedure performed (i.e. conventional surgery versus vitrectomy).*
   Patients undergoing retinal detachment surgery are asked to point to targets appearing on a computer touch screen, without being able to see their pointing hand. Comparisons of the horizontal pointing errors recorded pre-operatively and post-operatively are then made. A further comparison examining the effect of conventional external scleral buckling surgery versus vitrectomy is also made.

Part 2 of this thesis considers the role of extraocular muscle afferent signals in oculomotor control.

Part 3 of this thesis considers the role of extraocular muscle afferent signals in spatial localisation.

Part 4 of this thesis discusses the significance and implications of the findings presented in Parts 2 and 3.

PART 2 : THE ROLE OF EXTRAOCULAR MUSCLE AFFERENT SIGNALS IN OCULOMOTOR CONTROL

CHAPTER 5:
ASSESSMENT OF THE REPEATABILITY OF THE EYE MOVEMENT RECORDING

5.1 INTRODUCTION

Infrared oculography is a recognised method for recording eye movements [31]. This study used such a method in the form of an infra-red corneal reflection device (IRIS, Skalar Medical, Delft, Netherlands), a product which is well established for this purpose [114, 65, 86]. Despite this, it is still desirable to have an indication of its inherent variability and so an appraisal of the reliability of the method for repeated measurements of both saccades and smooth pursuit eye movements was carried out in a population of normal adults.

5.2 METHODS

All procedures conformed to the Declaration of Helsinki for research involving human subjects. Ethical committee approval was obtained and all participants gave informed consent.

5.2.1 Procedure

The horizontal movements (saccades and smooth pursuit) of the left eye were measured using the infra-red corneal reflection device. The right eye was occluded. Eye position signals were digitised at 1kHz with 12-bit precision using a CED μ1401 intelligent interface (Cambridge Electronic Design Ltd, Cambridge, UK). The eye position and a time marker of the appearance of the visual target were displayed on the computer screen; data from 100msec before, to 500msec after the appearance of the target was stored on disc for later analysis.

Saccade targets, generated by a CRS Visual Stimulus Generator (Cambridge Research Systems, Rochester, UK), were presented on a monitor which subjects viewed with their left eye from a distance of 57cm. Head movement was minimised by means of a chin rest and cheek pads. A fixation target appeared in

the centre of the screen for a random period of 0.5sec to 1.5sec. This was extinguished and replaced by a saccade target (0.3° black square on a light background) which was displayed for 200msec and appeared randomly at one of four locations, 5° or 10° to either the left or right of fixation. Targets were presented in two sessions of 52 trials. A short target presentation time and relatively small number of trials were used as this is equivalent to the protocol described in Chapter 6, and it was felt that the method to determine repeatability should be identical to the experimental paradigm. This is discussed further in Chapter 6.

Data were analysed off-line, using an analysis program, which displayed the time at which the target appeared, the recorded eye position and the calculated eye velocity. For each record in which target appearance was preceded by steady fixation, the amplitude, duration, peak velocity and latency of the primary saccade were measured (figure 1). Data from anticipatory saccades (i.e. latency <80msec) were not included in the analysis. A calibration factor was calculated from the first run by plotting the maximum gaze amplitude (i.e. primary plus subsequent corrective saccades when these occurred) of each individual trial against the target amplitude in degrees and using linear regression analysis to obtain the slope of the relationship.

The differences between the amplitudes, peak velocities, durations and latencies from the two sessions were calculated for individual subjects. These data were presented as the mean differences and the standard deviations of the mean differences [4]. The mean difference provides a measure of whether there is a consistent error in the results obtained between serial testing sessions. According to the British Standards Institution, 95% of differences in repeated measurements should be within 2 standard deviations (SD) of the mean difference [17]. This value is known as the repeatability coefficient and provides a measure of the reliability of the method. In addition, the amplitude-duration and amplitude-peak velocity relationships (otherwise known as the main sequence parameters [9]) were plotted for each session and compared. Statistical analysis was performed using GraphPad Software (CA, USA).

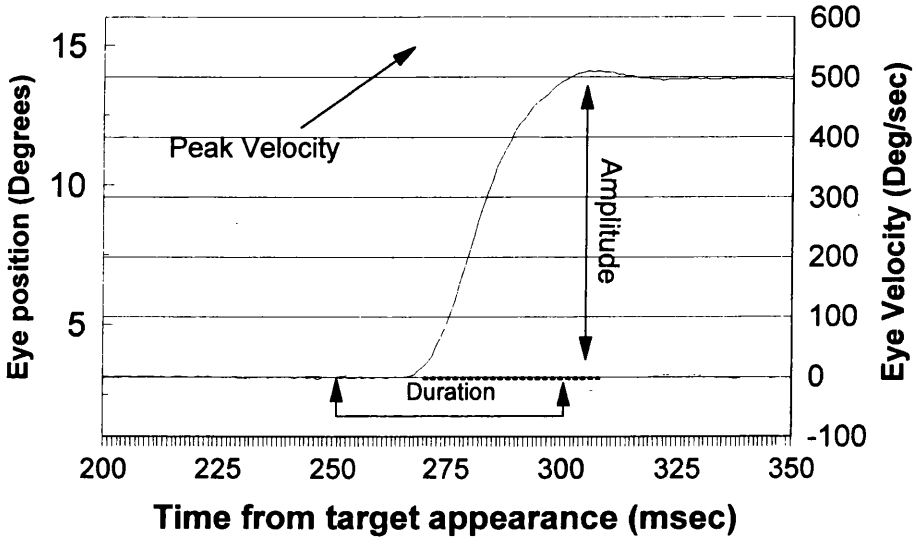

Figure 1 Eye position and eye velocity trace from which amplitude, peak velocity, duration and latency are calculated for individual saccades.

For smooth pursuit eye movements a step-ramp stimulus was presented to the left eye as follows: a central fixation target (generated by a CRS Visual Stimulus Generator) appeared on the monitor for a random period of 0.5sec-1.5sec. This was replaced by the smooth pursuit target which appeared randomly 5° to the right or left of fixation and then moved back through the centre of the display at a speed of 14°/sec. This task configuration ensured that the beginning of smooth pursuit was not obscured by the occurrence of an early saccadic eye movement [95]. Targets were presented in two sessions of 52 trials. This experimental protocol was chosen to be identical to that described in Chapter 7. This is discussed further in Chapter 7. The infrared corneal reflection device was calibrated at the beginning of each testing session as described above.

Data were analysed using an analysis program, which displayed the recorded eye positions, the calculated eye velocities and the times at which the pursuit target appeared. For each record in which target appearance was preceded by steady fixation, the initial acceleration and latency of the smooth pursuit response were calculated from traces of eye velocity (see figure 2). This was done as follows: two linear regression lines were fitted to velocity traces over a 50msec time period, the first one from 25msec before, to 25msec after the target appeared, and the second one during the acceleration phase of the response. The slope of this second line was used to calculate initial acceleration. The intercept between these two regression lines was taken as the time of smooth pursuit initiation. The peak velocity reached within 500msec of pursuit initiation was also recorded. The differences between the smooth pursuit parameters of the two runs were calculated for individual subjects. These results were presented as the mean differences and the standard deviations of the mean differences. The coefficient of repeatability was then calculated as outlined above.

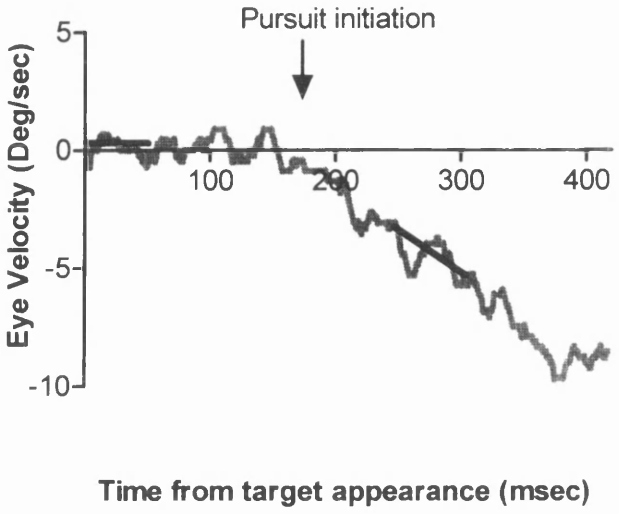

Figure 2 A typical smooth pursuit velocity profile. 2 regression lines are fitted to the trace as shown, and the initial acceleration is taken as the slope of the second line. Positive values for velocity represent movements from left to right and negative values represent movements from right to left.

5.2.2 Subjects

Six adult male subjects participated in this study (mean age 29 years, range 22-37 years). Their best corrected visual acuities were 6/6, N5 for each eye and none had any past ocular or medical history of note. Table 1 summarises their details. (Although this would appear to be a relatively small number of subjects, it should be noted that each testing session generates over one hundred individual trials, which are analysed in detail to yield considerable amounts of data).

Subject	Age	Distance acuity		Near acuity		Refraction	
		Right eye	Left eye	Right eye	Left eye	Right eye	Left eye
1	37	6 / 6	6 / 6	N5	N5	-2.75	-2.00
2	28	6 / 5	6 / 5	N5	N5	-0.50	-0.50
3	22	6 / 6	6 / 6	N5	N5	+0.25	+0.25
4	31	6 / 6	6 / 6	N5	N5	-1.00	-1.50
5	26	6 / 5	6 / 5	N5	N5	-0.75	-0.50
6	27	6 / 6	6 / 6	N5	N5	-0.25	-0.25

Table 1 Summary of details of the 6 control adults
Refractions are mean spherical equivalents (dioptres).

5.3 RESULTS

All subjects were able to execute saccades and smooth pursuit eye movements without any difficulty.

5.3.1 Saccades

The data from all subjects in response to targets moving to the right, and in response to targets moving to the left were pooled.

Table 2 summarises the results for saccade amplitude. The mean amplitudes over the two sessions in response to 5° and 10° targets were 5.2° (SD 0.5) and 10.3° (SD 0.7) respectively. The mean differences in amplitude between the two sessions were 0.3° (SD 0.2) and 0.7° (SD 0.3) for 5° and 10° targets respectively. The results from one subject are shown in figure 3. These are typical of the other subjects. The coefficient of repeatability for saccade amplitude (i.e. 2 x SD of mean difference between the two sessions) was 0.6°. According to the British Standards Institution, 95% of differences of serial measurements of saccade amplitudes are expected to be within 0.6° when using this technique. This means that a difference in saccade amplitude of greater than 0.6° between testing sessions indicates at least a 95% chance of the change being real.

Table 3 summarises the results for saccade peak velocity. The mean peak velocities over the two sessions in response to 5° and 10° targets were 235°/sec (SD 70) and 355°/sec (SD 80) respectively. The mean difference in peak velocities between the two sessions was 18°/sec (SD 5) and 17°/sec (SD 12) for 5° and 10° degree targets respectively. The results from one subject are shown in figure 4. These are typical of the other subjects. The coefficient of repeatability for saccade peak velocity was 20°/sec. 95% of differences of serial measurements of peak velocity are therefore expected to be within 20°/sec.

n=6	Target step				Overall
	5 degree		10 degree		
	Right	Left	Right	Left	
Mean saccade amplitude (1 + 2)	5.1	5.3	10	9.9	
SD	0.6	0.5	0.8	0.5	
95% Confidence Interval	4.4-5.8	4.7-5.8	9.2-11	9.4-10	
Mean difference (1 - 2)	0.4	0.3	0.6	0.8	**0.5**
SD	0.2	0.2	0.3	0.3	**0.3**
95% Confidence Interval	0.2-0.6	0.1-0.5	0.3-0.8	0.5-1.2	**0.4-0.6**
Paired t test (comparing 1 with 2)	p=0.6	p=0.6	p=0.5	p=0.3	**p=0.7**
Coefficient of repeatability					**0.6**

Table 2 **The repeatability of saccade amplitudes in 6 normal adults, comparing the first (1) and second (2) testing sessions. All values represent degrees.**

n=6	Target step				Overall
	5 degree		10 degree		
	Right	Left	Right	Left	
Mean peak velocity (1 + 2)	220	250	350	360	
SD	83	62	100	75	
95% Confidence Interval	130-310	180-310	240-460	280-430	
Mean difference (1 - 2)	21	16	22	13	**18**
SD	4	8	16	7	**10**
95% Confidence Interval	16-25	7-24	5-39	6.1-20	**14-22**
Paired t test (comparing 1 with 2)	p=0.8	p=0.8	p=0.9	p=0.9	**p=0.8**
Coefficient of repeatability					**20**

Table 3 **The repeatability of saccade peak velocity in 6 normal adults, comparing the first (1) and second (2) testing sessions. All values represent degrees/sec.**

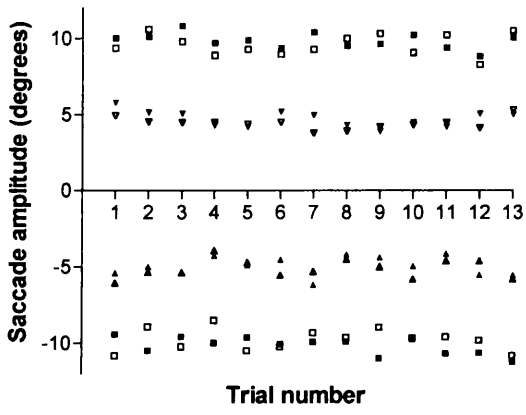

Figure 3 Trial by trial saccade amplitudes from one subject.

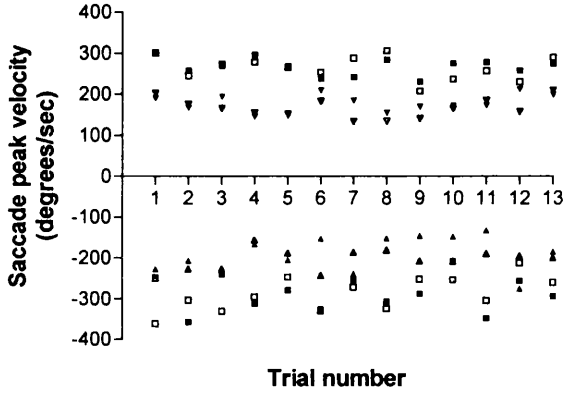

Figure 4 Trial by trial saccade peak velocities from one subject.

Figures 3 and 4 Trial by trial saccade parameters from one subject. Right and left 10 degree data are plotted as squares. Right and left 5 degree data are plotted as triangles. Filled symbols represent the first testing session and open symbols represent the second testing session. Positive values represent saccades to the right and negative values represent saccades to the left

Table 4 summarises the results for saccade duration. The mean duration over the two sessions in response to 5° and 10° degree targets were 43msec (SD 8.1) and 52msec (SD 9.5) respectively. The mean difference in duration between the two sessions was 2.1msec (SD 1.9) and 1.8msec (SD 1.4) for 5° and 10° targets respectively. The results from one subject are shown in figure 5. These are typical of the other subjects. The coefficient of repeatability for saccade duration was 4msec. 95% of differences of serial measurements of saccade duration are therefore expected to be within 4msec.

Table 5 summarises the results for saccade latency. The mean latency over the two sessions in response to 5° and 10° targets were 181msec (SD 36) and 190msec (SD 28) respectively. The mean difference in latency between the two sessions was 12msec (SD 7) and 15msec (SD 8) for 5° and 10° targets respectively. The results from one subject are shown in figure 6. These are typical of the other subjects. The coefficient of repeatability for saccade latency was 16msec. 95% of differences of serial measurements of saccade latency are therefore expected to be within 16msec.

Linear regression analysis showed that there was no significant difference in the amplitude-duration relationship ($p=0.75$, figure 7) or the amplitude-velocity relationship ($p=0.88$, figure 8) between the two testing sessions.

n=6	Target step				Overall
	5 degree		10 degree		
	Right	Left	Right	Left	
Mean saccade duration (1 + 2)	45	41	53	52	
SD	9.4	6.9	11	9.3	
95% Confidence Interval	35-55	34-49	41-64	4 2-61	
Mean difference (1 - 2)	2.7	1.5	2.3	1.3	2
SD	2.9	0.8	1.4	1.5	2
95% Confidence Interval	0.4-5.8	0.6-2.4	0.9-3.8	0.3-2.9	1.2-2.7
Paired t test (comparing 1 with 2)	p=0.8	p=0.7	p=0.9	p=0.8	p=0.9
Coefficient of repeatability					4

Table 4 The repeatability of saccade duration in 6 normal adults, comparing the first (1) and second (2) testing sessions. All values represent msec.

n=6	Target step				Overall
	5 degree		10 degree		
	Right	Left	Right	Left	
Mean saccade latency (1 + 2)	183	180	187	194	
SD	36	38	17	36	
95% Confidence Interval	146-221	140-220	169-204	156-231	
Mean difference (1 - 2)	13	11	18	12	14
SD	8	7	9	7	8
95% Confidence Interval	4.9-21	3.9-19	8.1-28	4.1-20	10.1-17
Paired t test (comparing 1 with 2)	p=0.7	p=0.9	p=0.6	p=0.8	p=0.9
Coefficient of repeatability					16

Table 5 The repeatability of saccade latency in 6 normal adults, comparing the first (1) and second (2) testing sessions. All values represent msec.

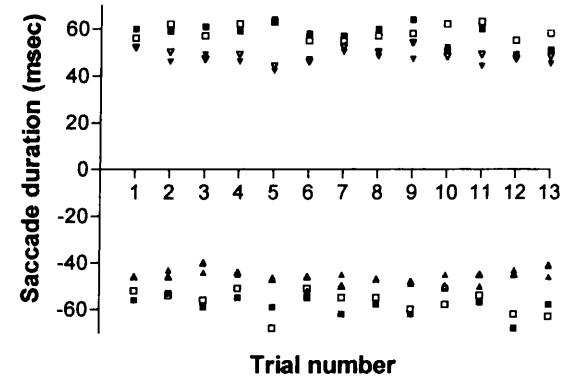

Figure 5 Trial by trial saccade durations from one subject.

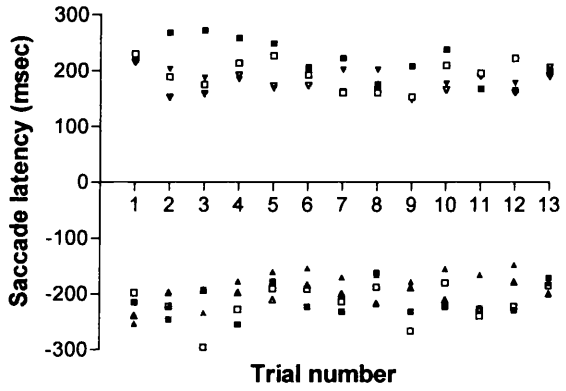

Figure 6 Trial by trial saccade latencies from one subject.

Figures 5 and 6 Trial by trial saccade parameters from one subject. Right and left 10 degree data are plotted as squares. Right and left 5 degree data are plotted as triangles. Filled symbols represent the first testing session and open symbols represent the second testing session. Positive values represent saccades to the right and negative values represent saccades to the left

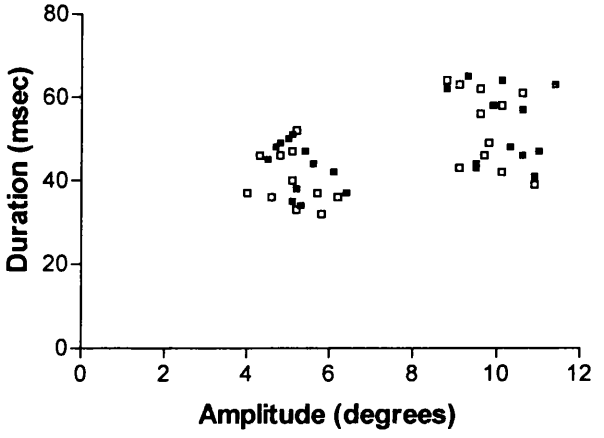

Figure 7 A comparison of the amplitude-duration relationships between the first (filled squares) and second (open squares) testing sessions. Note that there is no significant difference between the two (linear regression analysis F=0.1, p=0.75).

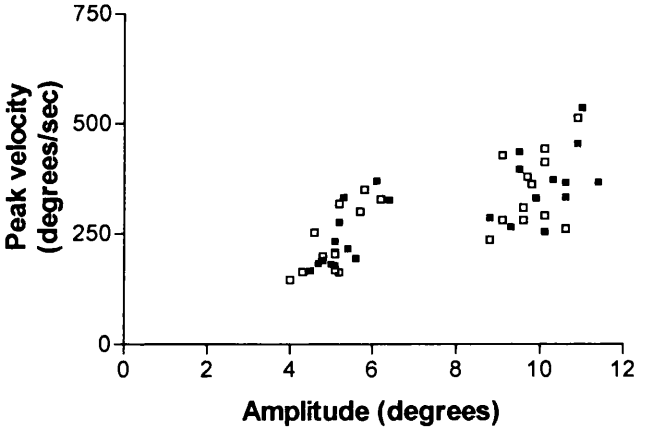

Figure 8 A comparison of the amplitude- peak velocity relationships between the first (filled squares) and second (open squares) testing sessions. Note that there is no significant difference between the two (linear regression analysis F=0.02, p=0.88).

5.3.2 Smooth Pursuit

The data from all subjects, in response to targets moving from right to left, and in response to targets moving from left to right, were pooled.

Table 6 summarises the results for smooth pursuit initial acceleration. The mean initial acceleration over the two sessions was 77°/sec/sec (SD 13) and the mean difference in initial acceleration between the two sessions was 6.8°/sec/sec (SD 4). The results from one subject are shown in figure 9. These are typical of the other subjects. The coefficient of repeatability for smooth pursuit initial acceleration was 8°/sec/sec. 95% of differences of serial measurements of initial acceleration are therefore expected to be within 8°/sec/sec.

Table 7 summarises the results for smooth pursuit peak velocity. The mean peak velocity over the two sessions was 12.5°/sec (SD 2.1) and the mean difference in peak velocity between the two sessions was 0.9°/sec (SD 0.6). The results from one subject are shown in figure 10. These are typical of the other subjects. The coefficient of repeatability was 1.2°/sec. 95% of differences of serial measurements of smooth pursuit peak velocity are therefore expected to be within 1.2°/sec.

Table 8 summarises the results for smooth pursuit latency. The mean latency over the two sessions was 170msec (SD 10) and the mean difference in latency between the two sessions was 13msec (SD 6). The results from one subject are shown in figure 11. These are typical of the other subjects. The coefficient of repeatability was 12msec. 95% of differences of serial measurements of smooth pursuit latency are therefore expected to be within 12msec.

n=6	Target direction		Overall
	Left-Right	Right-Left	
Mean initial acceleration (1 + 2)	78	77	**77**
SD	17	10	**13**
95% Confidence Interval	57-99	64-90	**68-87**
Mean difference (1 - 2)	7.4	6.2	**6.8**
SD	3.3	4.3	**4**
95% Confidence Interval	3.3-11	0.8-12	**4.2-9.4**
Paired t test (comparing 1 with 2)	p=0.9	p=0.7	**p=0.9**
Coefficient of repeatability			**8**

Table 6 **The repeatability of pursuit initial acceleration in 6 normal adults, comparing the first (1) and second (2) testing sessions. All values represent degrees/sec/sec.**

n=6	Target direction		Overall
	Left-Right	Right-Left	
Mean peak velocity (1 + 2)	13	12	**12.5**
SD	2.3	1.5	**2.1**
95% Confidence Interval	9.7-15	11.1-14	**10.9-14**
Mean difference (1 - 2)	0.7	1.2	**0.9**
SD	0.4	0.7	**0.6**
95% Confidence Interval	0.14-1.2	0.3-2.1	**0.5-1.4**
Paired t test (comparing 1 with 2)	p=0.8	p=0.5	**p=0.7**
Coefficient of repeatability			**1.2**

Table 7 **The repeatability of pursuit peak velocity in 6 normal adults, comparing the first (1) and second (2) testing sessions. All values represent degrees/sec.**

n=6	Target direction		Overall
	Left-Right	Right-Left	
Mean pursuit latency (1 + 2)	180	170	**170**
SD	6	13	**10**
95% Confidence Interval	170-180	150-180	**170-180**
Mean difference (1 - 2)	14	11	**13**
SD	5.4	7	**6**
95% Confidence Interval	6.2-12	6.4-14	**7.7-11**
Paired t test (comparing 1 with 2)	p=0.8	p=0.9	**p=0.8**
Coefficient of repeatability			**12**

Table 8 The repeatability of pursuit latency in 6 normal adults, comparing the first (1) and second (2) testing sessions. All values represent msec.

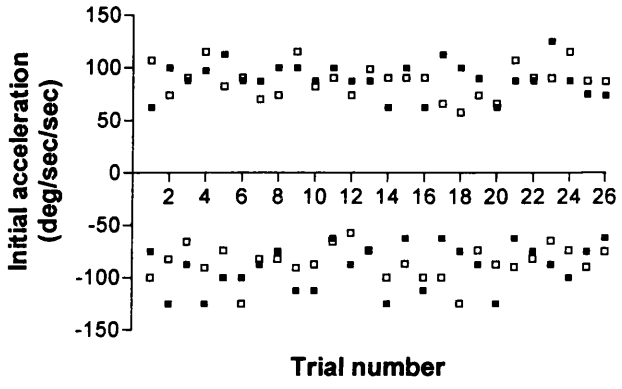

Figure 9 Trial by trial smooth pursuit initial accelerations from one subject.

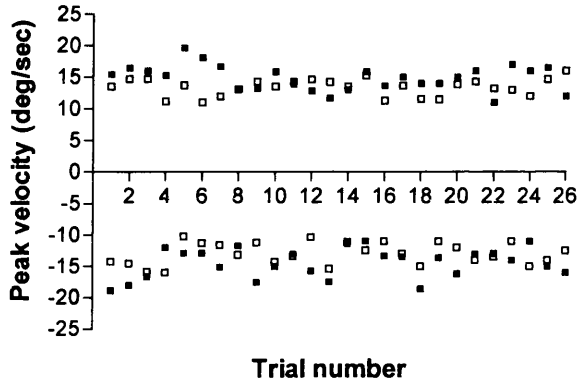

Figure 10 Trial by trial smooth pursuit peak velocities from one subject.

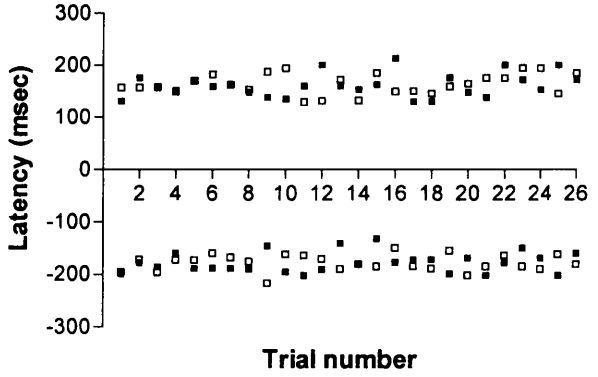

Figure 11 Trial by trial smooth pursuit latencies from one subject.

Figures 9 - 11 Trial by trial smooth pursuit parameters from one subject. Filled symbols represent the first testing session and open symbols represent the second testing session. Positive values represent trials in which the target moves from left to right, and negative values represent trials in which the target moves from right to left.

5.4 DISCUSSION

The saccade results demonstrate a high degree of consistency, particularly for the measurement of amplitude. In addition the peak velocity and duration measurements are comparable to recognised values [67]. The results for smooth pursuit, although showing a slightly greater variability, are also comparable to recognised values [67].

Overall, the coefficients of repeatability for the various parameters of saccades and smooth pursuit outlined above show that method used in this study is accurate and reliable for serial measurements of horizontal eye movements.

CHAPTER 6 :
MODIFICATION OF VISUALLY GUIDED SACCADES BY A NON-VISUAL AFFERENT FEEDBACK SIGNAL FROM THE CONTRALATERAL EYE

6.1 INTRODUCTION

For accurate monitoring and control of eye movement it might be thought that all possible sources of information would be utilised by the oculomotor system to determine eye position. However, as discussed in Chapter 2, although the extraocular muscles are richly endowed with intramuscular receptors [96, 74], it is generally accepted that afferent signals derived from these receptors are not involved in oculomotor control [16, 103]. This is despite the fact that experimentally modifying these proprioceptive signals using a single muscle vibration technique influences the programming of memory guided saccades [68], a finding which indicates that under certain circumstances the eye position information used by the oculomotor system is not only of central origin. One reason for discounting the role of afferent feedback in oculomotor control is that the extraocular muscles operate under conditions of a fixed load. Thus a given efferent signal always has a reliable and predictable effect on the position of the eyes, thereby eliminating the need for an afferent feedback signal. In this study, this condition was altered experimentally by impeding the movement of one eye to cause an acute increase in extraocular muscle load. This method is a modification of the passive eye movement technique discussed in Chapter 2, which is thought to alter non-visual afferent feedback from the extraocular muscles [48]. The effect of this on the movement of the contralateral eye during a visually guided saccade task was investigated to assess the response of the oculomotor system to such a perturbation.

6.2 METHODS

All procedures conformed to the Declaration of Helsinki for research involving human subjects. Local ethical approval was obtained for the study and all subjects participating gave their informed consent.

6.2.1 Procedure

A suction scleral contact lens was used to impede the movement of the right eye, while subjects performed a visually guided saccade task with the left eye. This has been described in detail previously by Al Hinnawi et al [2] and consists of an opaque 15mm diameter scleral contact lens with a 3mm peripheral flange. It is held in place using suction produced by a 20ml syringe connected to the lens via a soft silicone rubber tube, 1mm in diameter. The pressure beneath the lens is reduced by approximately 70mmHg, and is monitored carefully using a pressure gauge connected to the system. A stalk 3mm in diameter and 3cm in length is attached to the outer surface of the lens centrally and is placed in a custom built adjustable holder clamped to the experimental table. Whilst a small amount of slippage was observed, a very significant restriction of ocular movement was noted by the observers. This was deemed to be acceptable as the high levels of suction that would be required to completely abolish lens slippage have the potential to cause ocular damage. Thus with the lens in place, when subjects were asked to make voluntary horizontal saccades, the movement of the right eye was impeded.

The movements of the left eye were measured using the infrared corneal reflection device, which was described in Chapter 5. Saccade targets were generated as described in Chapter 5. The brief target presentation time of 200msec was used to ensure no retinal error signals were generated, particularly with the lens in place. Data were analysed a described in Chapter 5. Statistical analysis was performed using GraphPad Prism. Targets were presented in three runs of 52 trials for reasons discussed below. In the first and third runs the right eye was occluded but free to move, while in the second run movement of the right eye was impeded with the suction scleral lens. Prior to lens placement, several drops of local anaesthetic (Proxymetacaine Minims; Chauvin, Essex) were instilled in the right eye. The lens was then placed on the eye and gentle suction applied. The lens remained in place for no more than 5 minutes for reasons of safety. This in turn meant that the number of trials that could be performed within this time period was limited to 52. As there were two target steps for each direction (ie 5 and 10 degrees left and right), this resulted in 13 trials for each target step. Whilst the lens was in place the subjects were unable

to visualise the saccade targets on the monitor with their right eye. Once the experiment had been completed the subject's intraocular pressure was measured.

A control experiment was also performed, to assess the effect, if any, of the local anaesthetic drops on the saccadic movements of the contralateral eye. The procedure was identical to that described above, the only difference being that the lens was not placed in the right eye; it was occluded instead.

6.2.2 Subjects

Three adult male subjects were tested (PK, 37 years of age, RH, 31years of age and KB, 27 years of age). They all had a corrected visual acuity of 6/6, N5, and normal ocular motility. Their details are summarised in Table 9.

Subject	Age	Distance acuity		Near acuity		Refraction	
		Right eye	Left eye	Right eye	Left eye	Right eye	Left eye
1	37	6 / 6	6 / 6	N5	N5	-2.75	-2.00
2	31	6 / 6	6 / 6	N5	N5	-1.00	-1.50
3	27	6 / 6	6 / 6	N5	N5	-0.25	-0.25

Table 9 Summary of details of the 3 subjects for the saccade experiment. Refractions are mean spherical equivalents (dioptres).

6.3 RESULTS

Subjects executed monocular saccades to the briefly presented (200msec) targets with reasonable accuracy. When the right eye was impeded, subjects reported no discomfort and no perceived difficulty in either seeing the target with their left eye or executing saccades in response to the targets. Normality testing (Kolmogorov-Smirnov Test, Graph Pad Prism) confirmed a Gaussian distribution of the data, allowing parametric statistical tests to be performed.

When movements of the right eye were impeded the mean saccade amplitudes of the left eye were reduced in each of the three subjects in all experimental sessions. Figures 12 – 14 show data from each individual.

A similar pattern was observed when the pooled data were analysed. For example, for saccades executed in response to targets appearing 5° to the right of fixation, the mean pooled saccade amplitude was reduced by 23%, from 5.5° to 4.3° compared with the original level when the right eye was free to move (figure 15). This reduction was statistically significant (two sample t test, $p<0.001$, $t = 8.88$). For targets appearing 10° to the right of fixation the reduction in mean saccade amplitude was 22%, from 10.1° to 7.8° ($p<0.001$, $t = 11.57$). For targets appearing 5° to the left of fixation the reduction in mean saccade amplitude was 15%, from 5.2° to 4.4° ($p<0.001$, $t=5.39$). For targets appearing 10° to the left of fixation the reduction in mean saccade amplitude was 17%, from 9.7° to 8.1° ($p<0.001$, $t= 6.33$).

After the lens had been removed, the mean saccadic amplitudes of the left eye increased towards the normal (pre-lens) control values (figure 16). In response to targets appearing 5° and 10° to the right mean saccade amplitudes increased by 22% (two sample t test, $p<0.001$, $t=6.86$) and 25% ($p<0.001$, $t = 8.55$) respectively. In response to targets appearing 5° and 10° degrees to the left, mean saccade amplitudes increased by 7% ($p=0.03$, $t= 2.26$) and 11% ($p<0.001$, $t =3.52$) respectively.

After the suction contact lens had been removed the saccadic amplitudes sometimes remained slightly lower than the original amplitudes recorded before

the suction contact lens was inserted (figure 17). For the pooled data rightward saccade amplitudes for 5° targets and 10° targets remained 6% (two sample t test, $p=0.04$, $t=2.01$) and 4% ($p=0.07$, $t=1.88$) lower respectively than the pre-lens control values. Leftward saccade amplitude for 5° and 10° targets were 9% ($p=0.02$, $t=3.26$) and 8% ($p<0.001$, $t=3.54$) lower respectively.

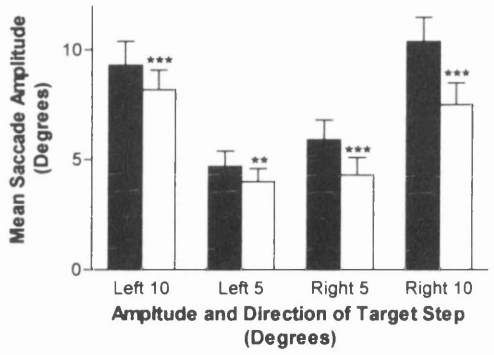

Figure 12 Data for subject PK.
(n=13 for each target step)

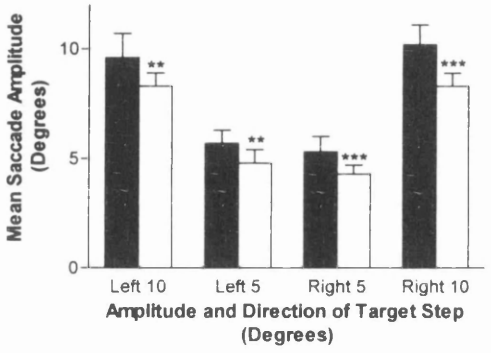

Figure 13 Data for subject KB.
(n=13 for each target step)

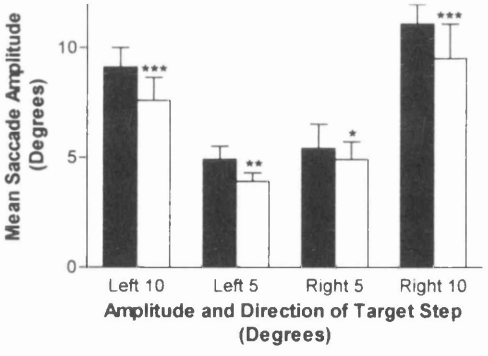

Figure 14 Data for subject RH.
(n=13 for each target step)

Figures 12 - 14 Comparisons of mean left eye saccade amplitudes for individual subjects before (black bars) and while (open bars) the right eye is impeded. Error bars represent standard deviations. Asterisks represent statistically significant differences (paired t test) between column pairs (***$p<0.001$; **$p<0.01$; *$p<0.05$).

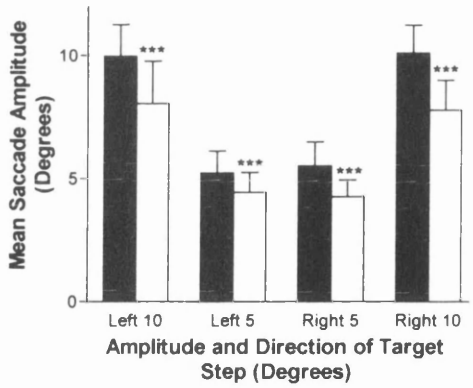

Figure 15 Data from before, and while the right eye is impeded.

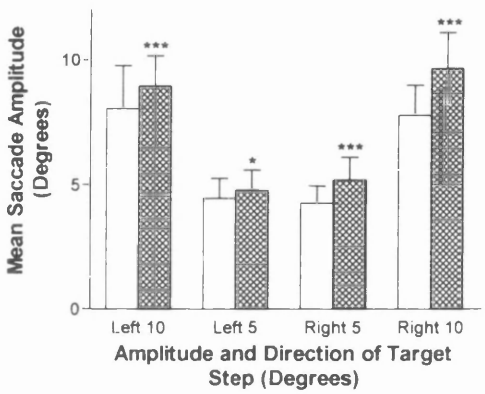

Figure 16 Data from while the right eye is impeded and after the lens has been removed.

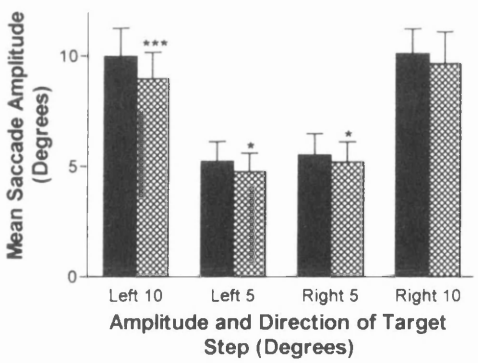

Figure 17 Data from before the right eye is impeded and after the lens has been removed.

Figures 15 - 17 Comparisons of mean left eye saccade amplitudes for pooled data (from all 3 subjects) before (black bars), whilst (open bars) and after (shaded bars) the right eye is impeded. Error bars represent standard deviations. Asterisks represent statistically significant differences (two sample t test) between column pairs (***$p<0.001$; **$p<0.01$; *$p<0.05$). n=3 for each target step.

Recording began within approximately 90 seconds of lens insertion in most runs, and on one occasion within less than 60 seconds. Figure 18 shows trial-by-trial mean amplitudes (data pooled across subjects and sessions). The pooled data are very similar to the individual data. Note that saccade amplitude was reduced in the first trial. Linear regressions of amplitude on trial number did not show any significant difference in the slope of the lines between the 'eye free' and 'eye impeded' conditions ($F=2$, $p=0.17$ and $F=1.5$, $p=0.2$ for the right 5° and 10° targets respectively; $F=1.6$, $p=0.23$ and $F=1.3$, $p=0.26$ for the left 5° and 10° targets respectively). Thus there was no evidence of a build up in the effect.

In addition, the amplitude-velocity relationship did not change. Typical data from one subject in a single experiment are plotted in figure 19. When the right eye was impeded the peak velocity of left eye saccades was no lower than would be predicted given the reduction in amplitude. There was no evidence from this analysis that saccade duration was modified inappropriately (figure 20). Thus while the amplitudes were reduced when the right eye was impeded, the velocity and duration scaled by a proportional amount. Impeding the movement of the right eye did not affect the latencies of left eye saccades. For example, for right 5° targets mean pooled latencies were 202msec (SD 47) and 198msec (SD 35) for the eye free and eye impeded conditions respectively. This difference was not statistically significant (two sample t test, $p=0.6$, $t=0.52$). For left 5° targets mean pooled latencies were 207msec (SD 52) and 214msec (SD 47) for the eye free and eye impeded conditions respectively ($p=0.4$, $t=0.8$). For right 10° targets mean pooled latencies were 199msec (SD 43) and 205msec (SD 48) for the eye free and eye impeded conditions respectively ($p=0.8$, $t=0.2$). For left 10° targets mean pooled latencies were 215msec (SD 51) and 209msec (SD 44) for the eye free and eye impeded conditions respectively ($p=0.5$, $t=0.6$).

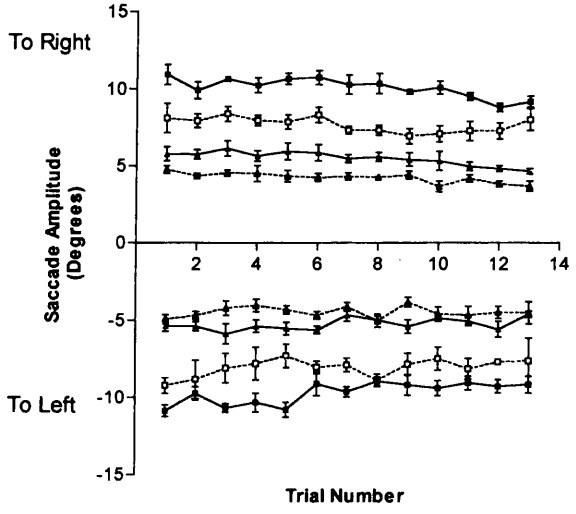

Figure 18
Trial by trial pooled mean left eye saccade amplitudes before (filled symbols) and whilst (open symbols) the right eye is impeded. Right and Left 10° data are plotted as squares; Right and Left 5 ° data are plotted as triangles. Positive values represent saccades to the right and negative values represent saccades to the left.
Note that the amplitude is reduced from the first trial and that there is little indication that the reduction builds up during the run. Error bars represent standard error of the mean. n=3 for each trial and target step.

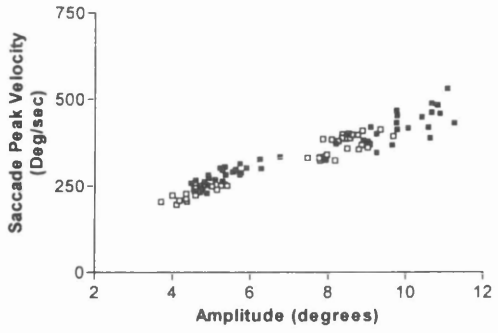

Figure 19 Typical individual subject data showing the relationship between saccade amplitude and saccade velocity before (filled symbols) and while (open symbols) the right eye is impeded. All correlation coefficients were statistically significant ($p<0.001$). Linear regressions of peak velocity on amplitude demonstrated no significant difference between 'eye free' and 'eye impeded' data. n=52.

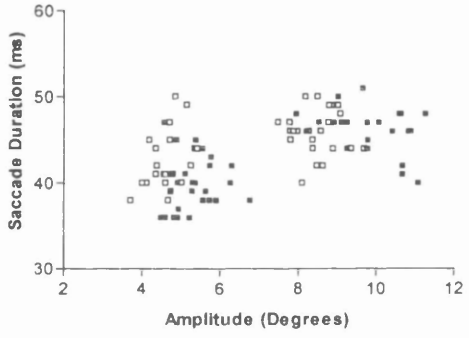

Figure 20 Typical individual subject data showing the relationship between saccade amplitude and saccade duration before (filled symbols) and while (open symbols) the right eye is impeded. All correlation coefficients were statistically significant ($p<0.001$). Linear regressions of duration on amplitude demonstrated no significant difference between 'eye free' and 'eye impeded' data . n=52.

The velocity profiles of saccades before and whilst the right eye was impeded were also examined. All profiles were aligned using the latency measurements; for two experiments in two subjects mean profiles were calculated (figures 21 – 23). Peak velocity when the right eye was impeded was lower as expected. The duration of these mean profiles was only slightly reduced. There was no evidence of the profiles being distorted in any way; the impeded profile diverged from the free profile at or near the beginning of the saccade. Examination of velocity profiles trial-by-trial confirmed that from the first trial there was a large reduction in peak velocity, with little evidence of further clear reductions.

The control experiment, which was performed with two subjects, showed that the local anaesthetic by itself did not cause a significant alteration in any of the saccade parameters of the contralateral eye, in particular there was no alteration in saccade amplitude (figure 24).

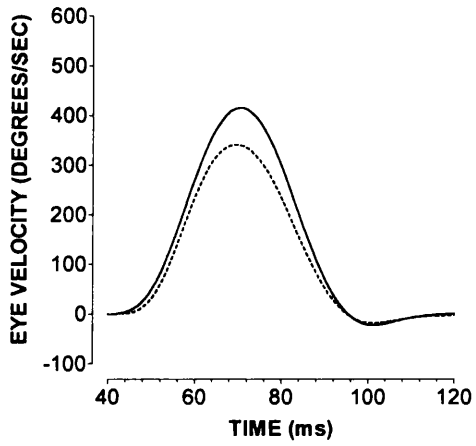

Figure 21 Mean velocity profiles before (solid line) and while (broken line) the right eye is impeded.

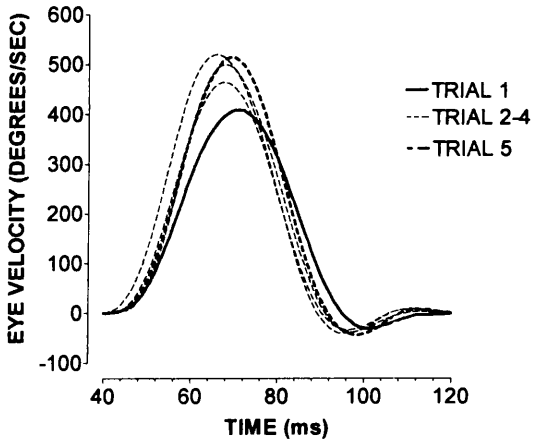

Figure 22 First 5 individual saccades before the right eye is impeded.

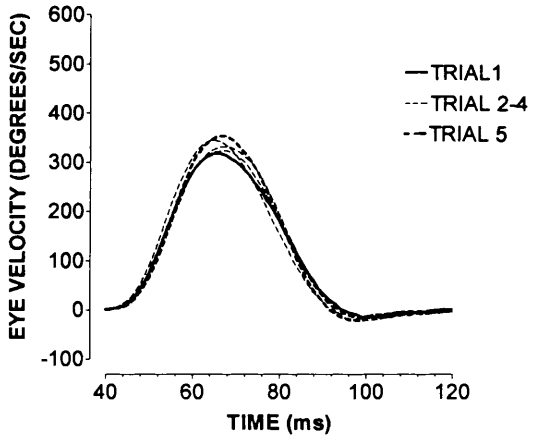

Figure 23 First 5 individual saccades while the right eye is impeded. Note that trial 1 peak velocity is reduced and that no further reduction is observed.

Figures 21 - 23. Typical saccade velocity profiles of the left eye, before and while the right eye is impeded. These data are from an individual subject in response to targets appearing 10 degrees to the right.

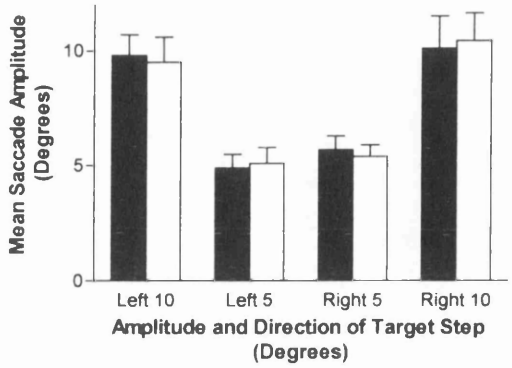

Figure 24 Comparisons of the mean left eye saccade amplitudes (from 2 subjects) for each of the four target positions before (black bars) and after (open bars) instillation of Proxymetacaine eye drops into the right eye. Note that there is no significant difference between the two conditions (two sample t test: for left 10 degrees p=0.5, t=0.7; for left 5 degrees p=0.6, t=0.5; for right 5 degrees p=0.6, t=0.5; and for right 10 degrees p=0.3, t=1.06).

6.4 DISCUSSION

The assumption that the extraocular muscles operate under a fixed load, coupled with the findings that not only do monkeys lack a monosynaptic stretch reflex [60], but that they can also execute accurate saccades when the extraocular muscles have been deafferentated [54] have been taken to justify the view that extraocular muscle afferent signals play little or no role, at least in the short term, in the control of eye movement. By impeding the movement of one eye, the load under which the extraocular muscles operate has been altered acutely, although to what extent is not known. Whilst a certain amount of slippage was observed beneath the contact lens, a definite restriction of movement was noted when compared with the contralateral eye. The results of this study show that under these specific circumstances the oculomotor system makes rapid adjustments. From the first trial in which the right eye was impeded, that is within a maximum of a few tens of seconds of lens placement, saccade amplitude in the contralateral eye was reduced. Note that this response is quite different from other types of adaptive response observed in the oculomotor system. These involve internal comparison of retinal information indicating a difference between desired and actual eye position [35] or retinal slip information [81]. In this experiment there was no retinal error because of the brief target presentation time. This ensured that when, in the impeded condition, the viewing eye landed short of the target position (as shown by the reduction in saccade amplitude), no retinal error was generated. It should be noted that the target presentation conditions did not vary between the "eye free" and "eye impeded" runs. As there was no gap between the fixation extinction and target presentation the testing protocol did not encourage the generation of express saccades, and in addition no difference in saccade latency was observed.

The clearest evidence of a response by the oculomotor system to impeding the movement of one eye was the effect on saccade amplitude. There was nothing to suggest that this built up over even a short period of a few seconds, or a small number of trials, although there was some evidence that when the lens was removed some residual amplitude reduction remained. Most examples of

adaptation of oculomotor parameters build up over a larger number of trials, or over a period of time during which adapting stimuli are presented. There was, however, no indication that each individual saccade was modified online. Had this been the case, one would have expected the velocity profiles of saccades in the impeded condition to diverge from the control profiles some short period after the beginning of the saccade. As figure 21 shows, this did not happen.
The finding of a reduction in saccade amplitude could be interpreted as showing that the saccade system seeks, at least in the circumstances used in these experiments, to preserve conjugacy. Thus as the right eye is not moving as far as intended, the drive to the left eye is reduced. It remains to be seen if the controller responds in this manner in different circumstances or when different types of eye movement (e.g. smooth pursuit) are manipulated. While saccade amplitude was clearly modified, the amplitude-velocity relationship was unaffected; the peak velocity of saccades in the impeded condition was reduced to the extent that might be predicted from the amplitude reduction. While no statistically significant alteration on the amplitude-duration relationship was found, the examination of the velocity profiles did suggest that the duration of saccades in the impeded condition was not as short as might be predicted.

This study has shown that there is a feedback signal, which in the absence of a retinal error signal induces alterations in visually guided saccades. In these experiments there was always a period of time between the placing of the lens and the beginning of the experimental run. However, this was kept a short as possible and was usually no longer than 90 seconds. During this time little specific visual information was available to aid any adaptive process. Any saccades executed were not responses to specific saccade targets, but voluntary saccades made on request to check the lens position. In the experimental run the amplitude effect was always present from the very first trial and did not subsequently build up (see figure 18). It seems highly unlikely that an adaptive process that began during the 90 second pre-run period would be completed by the end of the pre-run period. Rather the results are suggestive of the operation of a non-visual afferent signal, which detects that one eye is impeded and induces rapid modifications of the oculomotor system.

The impeded eye was anaesthetised, and while this does not rule out entirely the possibility of a mechanoreceptive source for these signals, this seems unlikely, particularly as local anaesthetic drops by themselves did not alter the saccadic response of the contralateral eye. It has also been suggested that periorbital receptors could be responsible for afferent feedback [84]. However, there is no direct evidence to support the existence of such receptors. On balance the most likely source for the effects we have observed are extraocular muscle proprioceptors. As discussed in Chapter 1 the human extraocular muscles are known to have relatively high numbers of muscle spindles [74] and also palisade endings, which may be unique to these muscles [103]. Single unit recording studies in various animal species have shown that afferent signals arising from extraocular muscle proprioceptors are able to modify the processing of information in the brainstem "on-line"; that is as soon as the afferent signals are induced, information processing is altered, it does not build up over a number of trials or cycles of stimulation [6, 36, 38]. However, if a feedback signal was acting on the brainstem gaze centres directly, modifications in the some of the main sequence parameters or their relationships would have been anticipated. Furthermore, if afferent signals were being distributed separately and directly to sub-areas of the horizontal gaze centre (e.g. to the burst generating circuitry in the *paramedian pontine reticular formation* and the integrator circuitry in the *nucleus prepositus hypoglossi*) mismatches between the saccade pulse and the saccade step might have been observed. There was no evidence of any of these. One can speculate therefore, that extraocular muscle afferent signals exert their effects at a higher level in the saccade control circuitry. Two candidate sites would be the cerebellum or superior colliculus, both of which are known to receive extraocular muscle afferent signals [39, 7, 66].

In summary, this study has demonstrated that experimentally impeding the movement of one eye can modify the visually guided saccades executed by the contralateral eye. This effect is due to an alteration in a non-visual afferent feedback signal, most likely to be derived from extraocular muscle proprioceptors.

CHAPTER 7:
MODIFICATION OF SMOOTH PURSUIT BY A NON-VISUAL AFFERENT FEEDBACK SIGNAL FROM THE CONTRALATERAL EYE

7.1 INTRODUCTION

The results from Chapter 6 demonstrate that experimental manipulation of afferent feedback signals from one eye modifies visually guided saccades of the contralateral eye, findings which highlight the ability of the oculomotor system to adapt rapidly in response to perturbations. However, it should be remembered that saccades are only one part of the human oculomotor repertoire. The output (ie position and motion) of other types of eye movement, such as smooth pursuit, also requires constant monitoring to ensure an optimal level of performance. As discussed in Chapter 2 the oculomotor system relies upon integration of both visual and non-visual information for this purpose, with the contribution of extraocular muscle afferent signals to the latter often discounted [16, 103]. This remains so despite reports that proprioceptive feedback can, when measuring eye velocity in the later stages of the smooth pursuit response, influence the adaptation of the system to changes in target velocity [114]. These findings were thought to be due to a reduction in the perceived extent of eye and target motion as a consequence of modified afferent input to the visual centres. However, nothing is known about the role of non-visual afferent signals in the earlier stages of the smooth pursuit response. Theoretically a non-visual feedback signal might aid pursuit performance during the initial open-loop phase when visual feedback is not available. To test this hypothesis the effect of manipulating extraocular muscle afferent signals on the initiation and early maintenance of smooth pursuit in human subjects was assessed by impeding the movement of one eye, and monitoring the response of the contralateral eye during step-ramp pursuit tasks.

7.2 METHODS

All procedures conformed to the Declaration of Helsinki for research involving human subjects. Local ethical approval was obtained for the study and all subjects participating gave their informed consent.

7.2.1 Procedure

The experimental procedure was very similar to that described in Chapter 6, the main difference being that subjects executed eye movements in response to smooth pursuit targets rather than saccade targets.

The movements of the left eye were measured using the infrared corneal reflection device as described in Chapter 5. Smooth pursuit targets were generated, and data analysed as described in Chapter 5. Targets were presented in three runs of either 52 trials for reasons discussed below. In the first and third runs the right eye was occluded but free to move, while in the second run the movement of the right eye was impeded with the suction scleral contact lens as described in Chapter 6. The lens remained in place for no more than 5 minutes for reasons of safety. This in turn meant that the number of trials that could be performed within this time period was limited to 52. As there was only one pursuit task in each direction this resulted in 26 trials for right to left targets, and 26 trials for left to right targets.

Smooth pursuit consists of two phases; approximately the first 100msec of pursuit is executed without the benefit of visual feedback (the open-loop period). Thereafter, pursuit can be modified by visual feedback and other non-retinal influences (closed-loop pursuit). In order to assess pursuit performance during both of these phases eye velocity was measured firstly at the end of the open-loop period 100msec after pursuit initiation, and secondly at 200msec, after an appreciable amount of "closed-loop" pursuit. Once pursuit is initiated, eye velocity often builds up to a peak before declining slightly and oscillating around the target velocity. Therefore, the maximum eye velocity that was reached within 500msec of pursuit initiation was also measured. Mean parameters were calculated and compared statistically using the paired, and two sample t-tests where appropriate.

A control experiment was also performed to assess the effect, if any, of the local

anaesthetic drops on the pursuit response of the contralateral eye. The procedure was identical to that described above, the only difference being that the lens was not placed in the right eye; it was occluded instead.

7.2.2 Subjects

Three adult male subjects were tested (PK, 37 years of age, RH, 31years of age and KB, 27 years of age). They all had a corrected visual acuity of 6/6, N5, and normal ocular motility. Their details are summarised in Table 10.

Subject	Age	Distance acuity		Near acuity		Refraction	
		Right eye	Left eye	Right eye	Left eye	Right eye	Left eye
1	37	6 / 6	6 / 6	N5	N5	-2.75	-2.00
2	31	6 / 6	6 / 6	N5	N5	-1.00	-1.50
3	27	6 / 6	6 / 6	N5	N5	-0.25	-0.25

Table 10 Summary of details of the 3 subjects for the pursuit experiment. Refractions are mean spherical equivalents (dioptres).

7.3 RESULTS

All subjects were able to execute smooth pursuit eye movements with reasonable accuracy. When the right eye was impeded, subjects reported no discomfort and no perceived difficulty in either seeing the target with the left eye. In addition, no obvious difference in fixation or the quality of pursuit was noted when compared with the control trials. As with the saccade experiment described in Chapter 6, whilst a small degree of slippage under the lens was noted, a significant restriction of movement was also observed. Normality testing (Kolmogorov-Smirnov Test, Graph Pad Prism) confirmed a Gaussian distribution of the data, allowing parametric statistical tests to be performed.

The mean initial acceleration of the left eye decreased significantly in all three subjects when the right eye was impeded using the suction contact lens. Data from individual subjects are shown in figures 25 - 27. For pursuit movements made in response to targets moving from right to left, the mean pooled acceleration (figure 28) decreased by 20% from 80°/sec/sec (SD 22) to 64°/sec/sec (SD18). This reduction was statistically significant (two sample t test, $p<0.001$, $t=5.6$). For pursuit movements made in response to targets moving from left to right, the mean pooled acceleration decreased by 17% from 82°/sec/sec (SD 19) to 68°/sec/sec (SD 16; $p<0.001$, $t=4.81$).

When the contact lens was removed the mean initial accelerations returned towards their original values. For example, in response to targets moving from right to left, it increased to 77°/sec/sec (SD 23.3). This was not significantly different from the pre-lens value (two sample t test, $p=0.33$; $t=0.42$). In response to targets moving from left to right, the initial acceleration increased to 80.5°/sec/sec (SD 17.3; $p=0.4$, $t=0.31$).

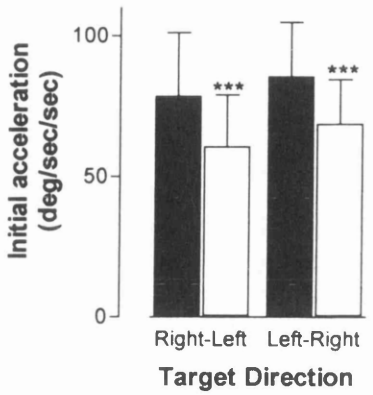

Figure 25 Data for subject PK.

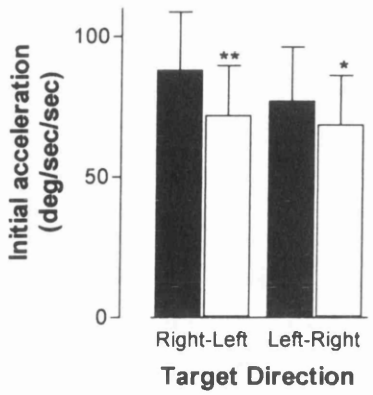

Figure 26 Data for subject JD.

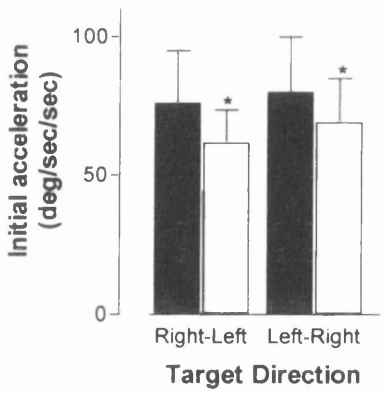

Figure 27 Data for subject KB.

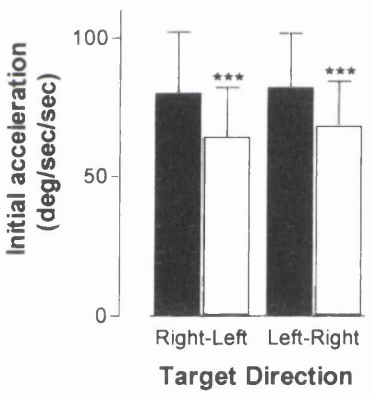

Figure 28 Pooled data from all three subjects.

Figures 25 - 28 Comparisons of mean smooth pursuit initial acceleration of the left eye before (black bars) and whilst (open bars) the right eye is impeded. Asterisks indicate statistically significant differences between column pairs. Paired t test for individual subjects, two sample t test for pooled data. (***$p<0.001$; **$p<0.01$; *$p<0.05$). Error bars represent standard deviations. n=26 for each target direction for individual subjects. n=3 for pooled data for each target direction.

As might be expected given the above results on eye acceleration, eye velocity during smooth pursuit initiation also decreased in all subjects when the right eye was impeded. The open loop velocity measured 100 ms after the initiation of pursuit, was reduced in all subjects (figures 29 - 31). For example in subject PK, this reduction was from 5.1°/sec (SD 1.4) to 4.2°/sec (SD 1.1; $p<0.001$, $t=3.49$) for targets moving from right to left, and from 5.5°/sec (SD 1.2) to 4.7°/sec (SD 1.1; paired t test, $p<0.001$, $t=3.63$; figure 29). For the pooled data, velocity at this point was reduced by 15% from 5.4°/sec (SD 1.6) to 4.6°/sec (SD 1.3; two sample t test, $p<0.001$, $t=3.52$) and by 11% from 5.4°/sec (SD 1.1) to 4.8°/sec (SD 1.2; $p<0.001$, $t=3.6$) in response to targets moving from right to left and from left to right respectively (figure 32).

When the contact lens was removed the velocity returned towards its original value. For example, in response to targets moving from right to left, it increased to 5.6°/sec (SD 1.5). This was not significantly different from the pre-lens value (two sample t test, $p=0.15$; $t=1.1$). In response to targets moving from left to right, it increased to 5.3°/sec (SD 1.3; $p=0.55$, $t=0.21$).

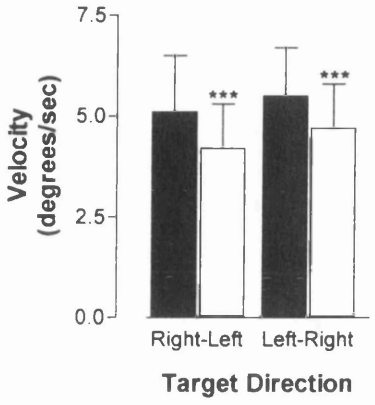

Figure 29 Data for subject PK.

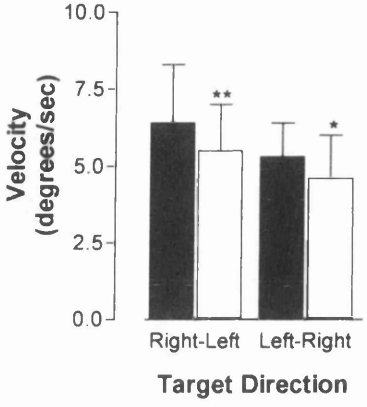

Figure 30 Data for subject JD.

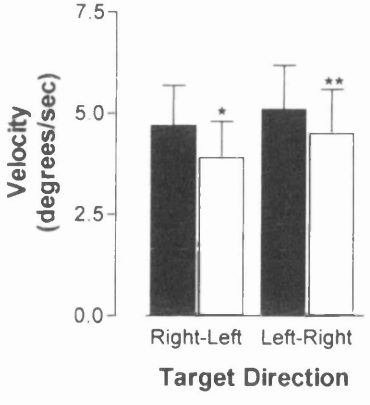

Figure 31 Data for subject KB.

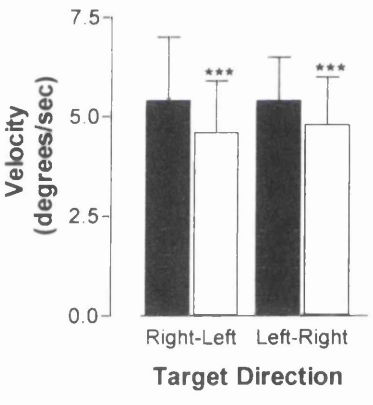

Figure 32 Pooled data from all three subjects.

Figures 29 - 32 Comparisons of mean velocity of the left eye 100msec after the initiation of smooth pursuit, before (black bars) and whilst (open bars) the right eye is impeded. Asterisks indicate statistically significant differences between column pairs. Paired t test for individual data, two sample t test for pooled data. (***$p<0.001$; **$p<0.01$; *$p<0.05$). Error bars represent standard deviations. n=26 for each target direction for individual subjects, n=3 for each target direction for pooled data.

200 ms after the initiation of pursuit (i.e. well into the closed loop phase), reductions in velocity were still observed when the right eye was impeded (figures 33 - 35). For example in subject PK, this reduction was from 12.8°/sec (SD 2.9) to 10.4°/sec (paired t test, SD 2.2; $p<0.001$, $t=4.66$) for targets moving from right to left, and from 13.4°/sec (SD 2.4) to 11.2°/sec (SD2.0; paired t test, $p<0.001$, $t=5.16$; figure 33). For the pooled data, the mean velocity was reduced by 14% from 12.8°/sec (SD 2.7) to 11°/sec (SD 2.4; two sample t test, $p<0.001$, $t=4.72$) and by 14% from 13.2°/sec (SD 2.3) to 11.4°/sec (SD 1.9; $p<0.001$, $t=5.22$) in response to targets moving from right to left and from left to right respectively (figure 36).

When the contact lens was removed the velocity measured at this time returned towards its original value. For example, in response to targets moving from right to left, it increased to 12.5°/sec (SD 2.9). This was not significantly different from the pre-lens value (two sample t test, $p=0.18$; $t=0.92$). In response to targets moving from left to right, it increased to 13.3°/sec (SD 2.6; $p=0.3$, $t=0.5$).

Peak velocity (the maximum eye velocity reached within 500ms of the initiation of pursuit) was also reduced in all subjects when the right eye was impeded. For the pooled data, the mean peak velocity was reduced by 17% from 14.3°/sec (SD 2.8) to 11.8°/sec (SD 2.6; two sample t test, $p<0.001$, $t=9.1$) and by 12% from 14.9°/sec (SD 2.6) to 13.1°/sec (SD 3.4; $p<0.001$, $t=5.87$) in response to targets moving from right to left and from left to right respectively (figure 37). When the contact lens was removed the peak velocity returned towards its original value. For example, in response to targets moving from right to left, it increased to 14.5°/sec (SD 3.0). This was not significantly different from the pre-lens value (two sample t test, $p=0.36$; $t=0.6$). In response to targets moving from left to right, it increased to 14.6°/sec (SD 2.5; $p=0.43$, $t=0.17$).

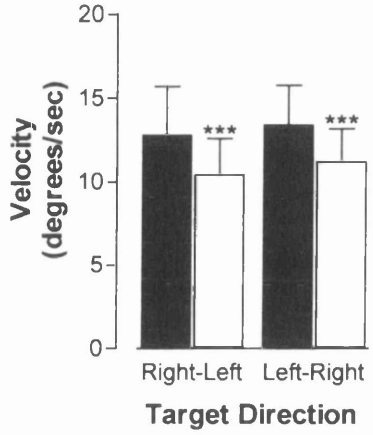

Figure 33 Data for subject PK.

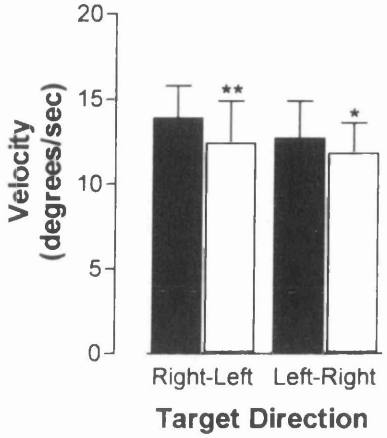

Figure 34 Data for subject JD.

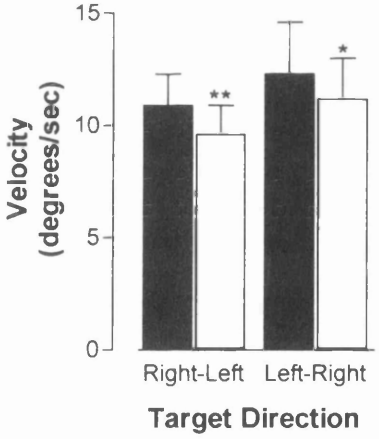

Figure 35 Data for subject KB.

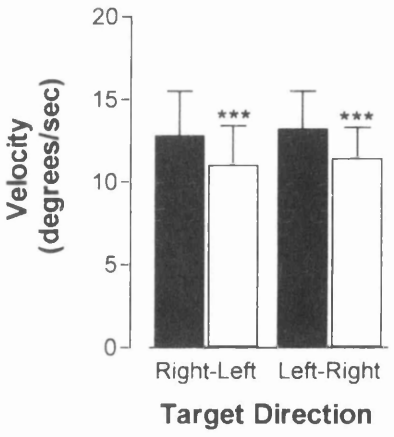

Figure 36 Pooled data from all three subjects

Figures 33 - 36 Comparisons of mean velocity of the left eye 200msec after the initiation of smooth pursuit, before (black bars) and whilst (open bars) the right eye is impeded. Asterisks indicate statistically significant differences between column pairs. Paired t test for individual subjects, two sample t test for pooled data. (***$p<0.001$; **$p<0.01$; *$p<0.05$). Error bars represent standard deviations. n=26 for each target direction for individual subjects, n=3 for each target direction for pooled data.

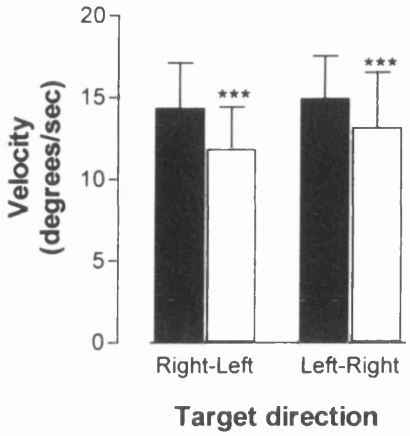

Figure 37 A comparison of peak pursuit velocities of the left eye before (black bars) and while (open bars) the right eye is impeded. These plots represent the means of pooled data from all three subjects. Asterisks indicate statistically significant differences between column pairs (two sample t test; ***$p<0.001$). Error bars represent standard deviations.

These reductions in pursuit velocity were observed from the first trial when the right eye was impeded. Figures 38 and 39 show trial by trial mean velocities (data pooled across subjects and sessions) at both 100msec and 200msec after the initiation of pursuit respectively. Individual data are similar. Linear regressions of velocity on trial number did not show any significant difference in the slope between the 'eye free' and 'eye impeded' conditions (for 100msec data $F=0.7$, $p=0.4$; for 200msec data $F=0.8$, $p=0.5$). Thus there was no evidence for a build up in the effect.

The latency of the smooth pursuit response was unaffected by impeding the movement of the right eye. For example, in response to targets moving from right to left, the mean latencies were 176msec (SD 20) and 179msec (SD 25), before and whilst the eye was impeded respectively (two sample t test, $p=0.9$; $t=0.1$). In response to targets moving from left to right, the mean latencies were 169msec (SD 22) and 165msec (SD 17), before and whilst the eye was impeded respectively ($p=0.15$; $t=1.13$).

The control experiment, which was performed with two subjects, showed that the local anaesthetic by itself did not cause a significant alteration in any of the parameters of smooth pursuit eye movements of the contralateral eye (figures 40 and 41).

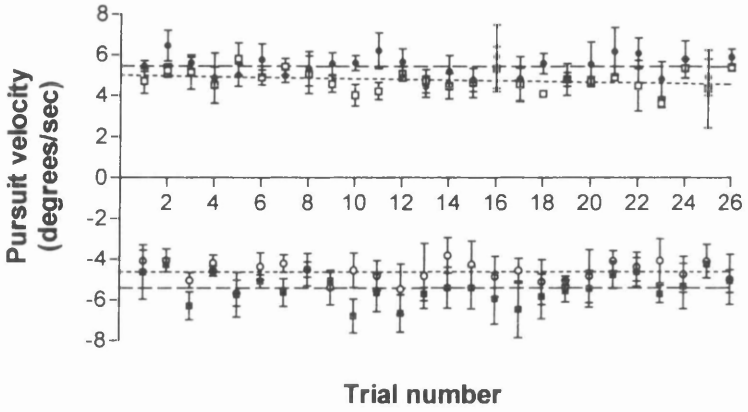

Figure 38 Data 100msec after the initiation of smooth pursuit.

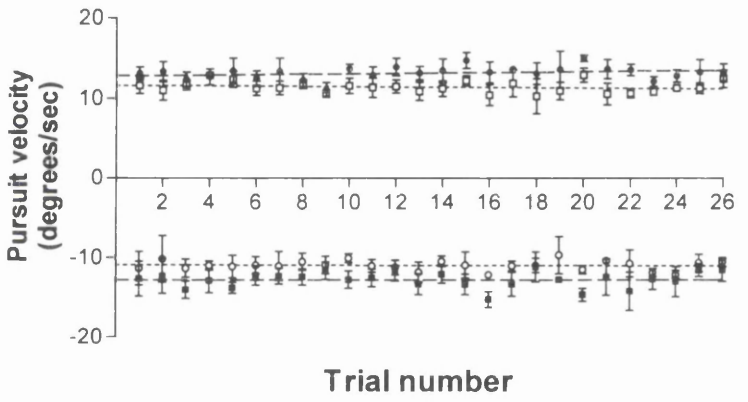

Figure 39 Data 200msec after the initiation of smooth pursuit.

Figures 38 - 39 Trial by trial pooled mean velocities of the left eye 100msec and 200msec after the initiation of pursuit, before (filled symbols) and whilst (open symbols) the right eye is impeded. Positive values represent trials inwhich the target moves from left to right, and negative values represent trials in which the target moves from right to left. Note that the velocities are reduced from the first trial and that there is no indication that the reduction builds up during the run. Error bars represent standard error of the mean. n=3 for each trial for each target direction.

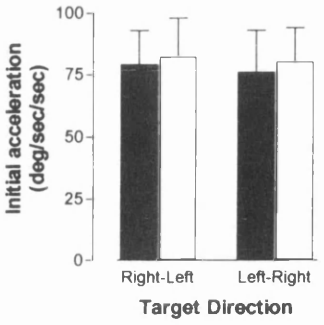

Figure 40. Comparison of the mean initial acceleration. Note that there is no significant difference between the column pairs (two sample t test p=0.7, t=0.5 for targets moving from right to left, and p=0.8, t=0.3 for targets moving from left to right).

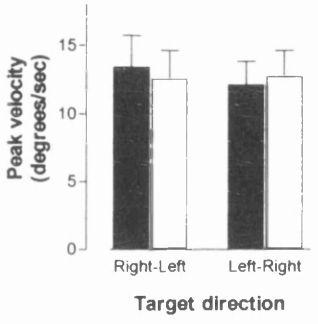

Figure 41. Comparison of the mean peak velocity. Note that there is no significant difference between the column pairs (two sample t test, p=0.3, t=1.1 for targets moving from right to left, and p=0.5, t=0.7 for targets moving from left to right).

Figures 40 - 41. Comparisons of the mean initial acceleration, and the mean peak velocity of the left eye, before (black bars) and after (open bars) instillation of Proxymetacaine eye drops into the right eye. Data is pooled from both subjects.

7.4 DISCUSSION

These results show that impeding the movement of one eye leads to small but consistent alterations in the initiation and early maintenance of pursuit movements of the contralateral eye. Both the initial acceleration and the peak open loop velocity were reduced by a statistically significant amount. These parameters provide a measure of the performance of the pursuit system in the absence of either retinal (visual) feedback or internal representations of target trajectory. No evidence was found to suggest that the effects built up over time or during initial trials; they were present from the first trial in which the eye was impeded. Given that latency was unaffected, it seems unlikely that subjects had any difficulty seeing target motion and extracting useful information from it. Had impeding one eye altered motion thresholds, then an increase in pursuit latency would have been expected. Therefore the changes that were observed are consistent with the hypothesis of an extraretinal signal acting on the pursuit system itself, as opposed to the visual inputs driving the pursuit response.

Both the velocity 200msec after pursuit was initiated, as well as the peak velocity, were reduced when the contralateral eye was impeded. From approximately 100msec after pursuit is initiated retinal feedback is available to indicate the accuracy of the pursuit response. This information could, in theory, be utilised to provide an error signal indicating that velocity in the free eye was inadequate, thereby allowing a compensatory response (i.e. increasing velocity) to be initiated. However, there was no evidence of such a response. On the contrary, there was actually a reduction in eye velocity of 14% at 200msec for targets moving in both directions, and of 17% and 12% in peak velocity for targets moving to the left and right respectively. But a number of factors must be borne in mind when interpreting these results. With a target velocity of 14°/s the observed reductions in peak eye velocity imply a retinal slip velocity of 1.68°/s and 2.4°/s (for leftward and rightward targets respectively) over, at most, a few tens of milliseconds. It may be that these errors are not of a sufficient magnitude to trigger alterations in pursuit. If they had persisted (i.e. if subjects had been exposed to longer trajectories of target motion) the most likely effect would have been the occurrence of saccades to correct the growing position error.

Alternatively, even with short target trajectories, had the subjects been exposed to larger trial numbers an adaptation of the pursuit system may have been observed [46].

What is the cause of these modifications in the smooth pursuit response of the contralateral eye? The most plausible explanation is that impeding the movement of one eye induces a non-visual afferent signal which indicates to the oculomotor control system that the impeded eye is moving more slowly than it otherwise should. As with the saccade studies described in Chapter 6, the fact that the local anaesthetic by itself had no effect on the response of the contralateral eye suggests that this signal did not originate from ocular surface receptors. The most likely source comprise the extraocular muscle sensory receptors. Certainly afferent signals from the extraocular muscles are known to carry information concerning eye position and velocity in a wide range of species [27, 29, 42]. In addition, these signals are capable of altering the central processing of visual, vestibular and oculomotor information. It is not clear why, under these circumstances, the oculomotor control system should seek to reduce eye velocity in the contralateral eye. However, it would appear that for both the pursuit and saccadic systems (see Chapter 6), the priority is to maintain conjugacy.

Van Donkelaar et al [114] also used a suction contact lens system to hold one eye in the primary position during a pursuit visual adaptation paradigm, and by doing so demonstrated a modification in the normal adaptive processes of the contralateral eye. They concluded that extraocular muscle afferent signals provide information concerning eye and target motion, which is necessary for the normal operation of the pursuit system. While their approach was clearly different from that of this study, their results do appear to be complementary.

The exact site or sites within the central nervous system where extraocular muscle afferent feedback could influence the smooth pursuit system is not known. However, the unexpected finding that impeding one eye reduces the drive from the oculomotor system during pursuit strongly parallels the earlier results on saccades (see Chapter 6). There it was found that when one eye was

impeded the saccade amplitude in the contralateral eye was reduced, while the main sequence relationships were unaltered. This suggested a signal acting above the brainstem gaze centres perhaps at the level of the superior colliculus or cerebellum, both of which receive afferent signals from the extraocular muscles [1, 10, 39, 62]. Of these two, the structure that plays a central role in the control of both saccade amplitude and smooth pursuit is the cerebellum. Interestingly, new models of both the saccade [94] and pursuit [61] control systems incorporate cerebellar monitoring of oculomotor performance, with the latter [61] also including a role for extraocular muscle proprioception in providing eye position and velocity information via mossy fibre input. Although their model relates to predictive targets rather than the randomised step-ramp target trajectories used in this study, it does add weight to the evidence presented here that extraocular muscle afferent feedback contributes to the generation and control of smooth pursuit eye movements.

In summary, this study has demonstrated that experimentally impeding the movement of one eye can modify smooth pursuit eye movements executed by the contralateral eye. This effect is thought to be due to an alteration in a non-visual afferent feedback signal, most likely to be derived from extraocular muscle proprioceptors. These findings provide further evidence supporting the role of extraocular muscle afferent signals in human oculomotor control

PART 3 : THE ROLE OF EXTRAOCULAR MUSCLE AFFERENT SIGNALS IN SPATIAL LOCALISATION

CHAPTER 8:
ASSESSMENT OF SPATIAL LOCALISATION IN A NORMAL POPULATION

8.1 INTRODUCTION

Pointing to targets appearing on a screen without vision of the pointing hand is a standard method for assessing spatial localisation in children and adults [112, 48, 33, 55]. As discussed in Chapter 3 a combination of retinal and extraretinal information is utilised to determine the location of the object of interest, and when we then require to reach out or point to this object, an appropriate motor command is sent to the arm and hand which enables us to perform the task efficiently. By preventing vision of the pointing hand (thereby eliminating visual feedback) the extraretinal source of information becomes increasingly important. Although the method used in this study to test spatial localisation is similar to that described in previous reports [112, 33], it is still desirable to have an indication of its inherent variability, particularly when performing serial assessments. In view of this, an appraisal of the reliability of the method for repeated measurements was carried out, for a normal population of both children and adults.

8.2 ASSESSMENT OF REPEATABILITY OF SPATIAL LOCALISATION IN CHILDREN

8.2.1 METHODS

All procedures conformed to the Declaration of Helsinki for research involving human subjects. Ethical committee approval was obtained and parental informed consent was given in all cases.

Procedure

Each subject was seated and viewed a computer touchscreen (IBM, Greenock, UK; luminance 57 cd/m^2) from a distance of 26.5cm. The head was stabilised using chin rests and cheek pads. Pictures of three vertical poles were presented

on the screen, in the centre and 20 degrees to the left and to the right of centre respectively (figure 42). A green target (a 'dragon', 4cmx 2cm, luminance 45 cd/m^2) appeared on the top of one pole and the subject was asked to touch the screen at the bottom of the pole on which the 'dragon' had landed with the outstretched index finger of the dominant hand. The 'dragon' then jumped randomly to the top of another pole and the subject was asked to touch the location of this pole. No limit of time was placed on the pointing response. The target was presented on ten separate occasions to each pole and the location of each pointing response was stored online for later analysis. The disparity between the true location and the mean touched location of the ten presentations was taken as the horizontal pointing error for that pole. A trial run was allowed in which the subject could visualise their pointing hand to enable him/her to become familiar with the testing procedure. A cardboard sheet covered with black cloth was then used to mask the lower part of the screen thereby preventing the subject from seeing their pointing hand. They were allowed to practise with this in place. The formal testing session then commenced. Each subject was tested whilst viewing binocularly, and then monocularly using the right eye only. (Only one eye was tested to limit the time taken and thereby maintain a good level of concentration and compliance). To minimise any bias due to a learning effect a coin was tossed to determine which condition was tested first. After the first testing session had been completed it was then repeated in the same order.

The difference between the horizontal pointing errors for the two sessions, both for the binocular and monocular conditions, was calculated for individual subjects for each pole. These results are presented as the mean difference and the standard deviation of the mean difference. From this the repeatability coefficient is calculated as described in Chapter 5. Statistical analysis was performed using GraphPad Prism.

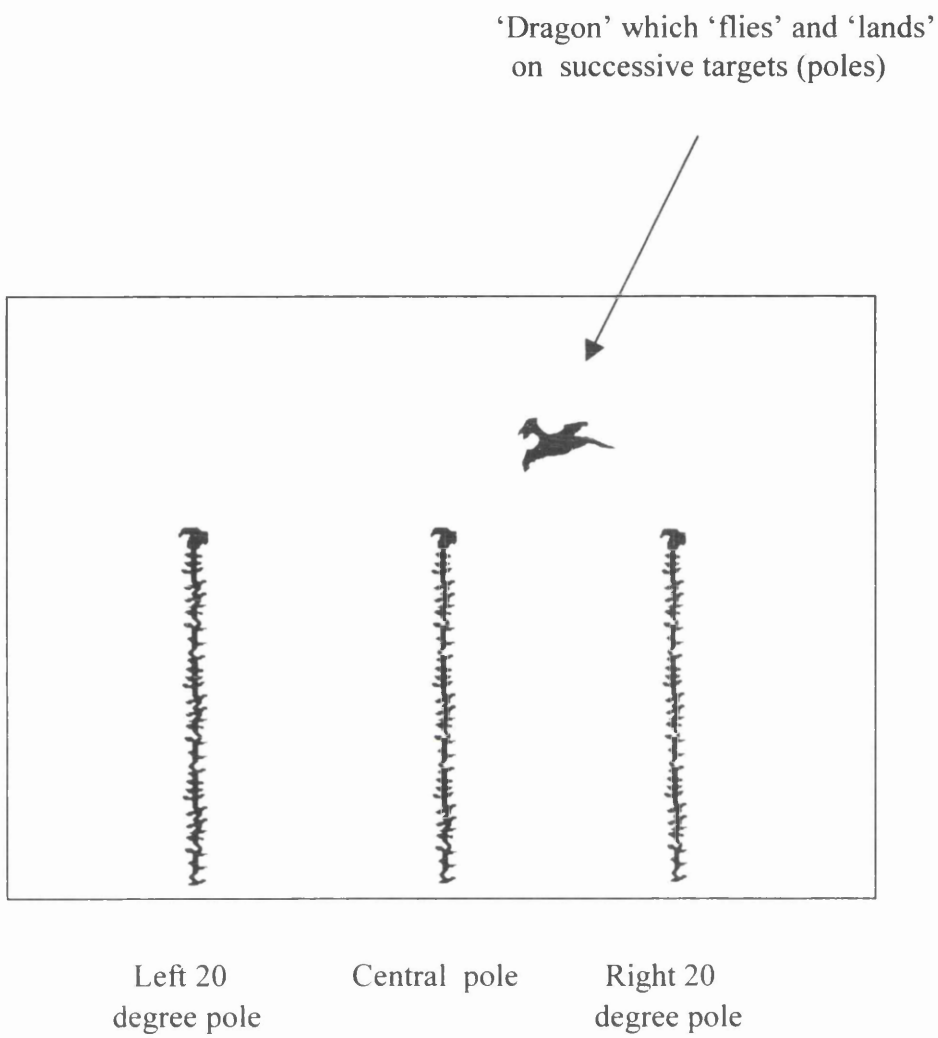

Figure 42 A diagram showing the computer touchscreen

Subjects

20 subjects (10 male, 10 female) were tested and comprised children attending the Orthoptic Clinic at Gartnavel General Hospital for visual screening, as well as children of friends and relatives of the author. They had a mean age of 5 years and 4 months (SD 11 months; range 4 years and 6 months to 7 years). These data are summarised in Table 11. None had any prior ocular history and no prior history of neurological or musculoskeletal problems. No children had any significant refractive error and no evidence of amblyopia as defined by a uniocular visual acuity of less than 0.250 (logMAR) or an interocular acuity difference of greater than 0.1 log units[106]. None had any evidence of a manifest strabismus. Visual acuities were recorded unaided using logMAR crowded tests at a distance of 3 metres [79] and MacLure Reading Type for Children, at a distance of 25cm.

Subject	Age	Distance acuity (LogMar)		Near acuity	
		Right eye	Left eye	Right eye	Left eye
1	4 yrs 6 mths	0.05	0.025	N5	N5
2	5 yrs	0	0	N5	N5
3	4 yrs 8 mths	0.025	0.025	N5	N5
4	5 yrs	-0.025	0.025	N5	N5
5	4 yrs 6 mths	0.1	0.125	N5	N5
6	5 yrs	0.075	0.1	N5	N5
7	5 yrs 4 mths	0.05	0.05	N5	N5
8	4 yrs 7 mths	0.025	0	N5	N5
9	4 yrs 6 mths	0.125	0.1	N5	N5
10	4 yrs 6 mths	0.1	0.1	N5	N5
11	6 yrs	0.075	0.075	N5	N5
12	6 yrs 4 mths	0.05	0.075	N5	N5
13	6 yrs 4 mths	0.075	0.1	N5	N5
14	7 yrs	0.05	0.05	N5	N5
15	5 yrs 3 mths	0.05	0.05	N5	N5
16	5 yrs 3 mths	0.075	0.075	N5	N5
17	5 yrs	0.025	0.075	N5	N5
18	6 yrs 9 mths	0.025	0.025	N5	N5
19	5 yrs 8 mths	0.075	0.075	N5	N5
20	7 yrs	0.1	0.075	N5	N5

Table 11 Summary of details of the 20 control children

8.2.2 RESULTS

All of the children were able to perform the test without any difficulty. The mean distance visual acuity was 0.06 log units (SD 0.04) for both the right and left eyes. The near visual acuity was N5 for both the right and left eyes for all subjects. Normality testing (Kolmogorov-Smirnov Test, Graph Pad Prism) confirmed a Gaussian distribution of the pointing responses, allowing parametric statistical tests to be performed on the data.

Binocular Results

Table 12 summarises the results for children viewing binocularly. The overall mean pointing error (i.e. for all 3 poles) over the two testing sessions was 3.8 degrees (SD 1.9). The overall mean difference in pointing response between the two sessions was 0.9 degrees (SD 0.45). The coefficient of repeatability for pointing response (i.e. 2 x SD of mean difference) was 0.9 degrees. No relationship was found between differences in pointing response and pointing error for individual subjects ($r=0.2$, $p=0.1$; figure 43). No correlation was found between subject age and pointing error ($r=0.1$, $p=0.6$; figure 44), or subject age and difference in pointing response ($r=0.19$, $p=0.4$; figure 45).

n = 20	Pole location			
	Left 20°	Central	Right 20°	Overall
Mean pointing error (1 + 2)	3.9	3.4	3.9	**3.8**
SD	1.9	1.7	2.2	**1.9**
95% Confidence Interval				**3.3 - 4.2**
Mean difference (1 - 2)	1	0.9	0.9	**0.9**
SD	0.5	0.4	0.5	**0.45**
95% Confidence Interval				**0.7 - 1.0**
Paired t test (comparing 1 with 2)	p=0.6	p=0.7	p=0.6	**p=0.7**
Coefficient of repeatability				**0.9**

Table 12 **The repeatability of pointing responses in 20 normal children when viewing binocularly comparing the first (1) and second (2) testing sessions. All values represent degrees.**

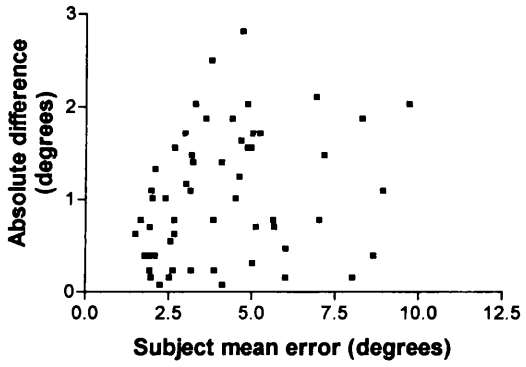

Figure 43 A plot showing the absolute difference in pointing responses between the first and second testing sessions versus the mean pointing error for individual subjects. Data is for all 20 control children, for all 3 pole locations, when viewing binocularly. Note that is no correlation between the two (r=0.2, p=0.1).

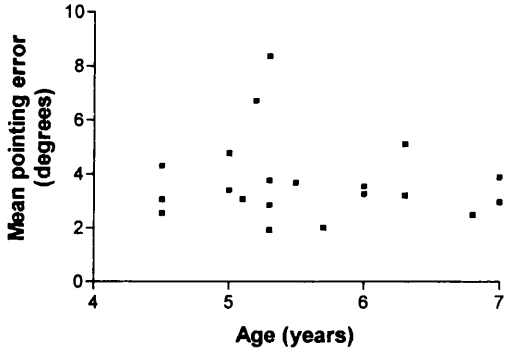

Figure 44 A plot showing the mean pointing error versus age of individual subjects. Data is for all 20 control children when viewing binocularly and pooled for all 3 pole locations. Note that there is no correlation between the two (r=0.1, p=0.6).

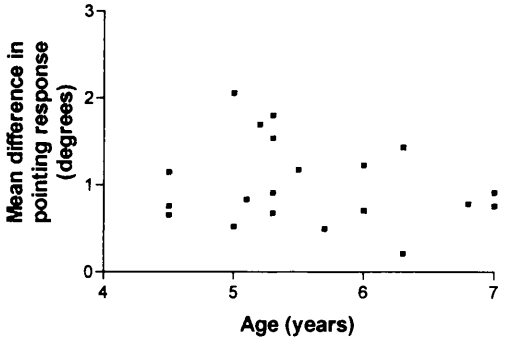

Figure 45 A plot showing the mean difference in pointing response between the first and second testing sessions versus age of individual subjects. Data is for all 20 control children when viewing binocularly and pooled for all 3 pole locations. Note that there is no correlation between the two (r=0.19, p=0.4).

Monocular Results

Table 13 summarises the results for children viewing monocularly. The overall mean pointing error for the two testing sessions was 3.9 degrees (SD 1.6). The overall mean difference in pointing response between the two sessions was 0.9 degrees (SD 0.5). The coefficient of repeatability for pointing response was 1 degree. No relationship was found between differences in pointing response and pointing error for individual subjects ($r=0.17$, $p=0.19$; figure 46). No correlation was found between subject age and pointing error ($r=0.15$, $p=0.5$; figure 47), or subject age and difference in pointing response ($r=0.14$, $p=0.6$; figure 48).

n=20	Pole location			Overall
	Left 20°	Central	Right 20°	
Mean pointing error (1 + 2) **SD** **95% Confidence Interval**	4 1.8	3.7 1.2	3.9 1.7	**3.9** **1.6** **3.5 - 4.4**
Mean difference (1 - 2) **SD** **95% Confidence Interval**	1.1 0.5	1 0.4	1.2 0.6	**0.9** **0.5** **0.8 - 1.2**
Paired t test (comparing 1 with 2)	p=0.4	p=0.5	p=0.6	**p=0.5**
Coefficient of repeatability				**1**

Table 13 The repeatability of pointing responses in 20 normal children when viewing monocularly comparing the first (1) and second (2) testing sessions. All values represent degrees.

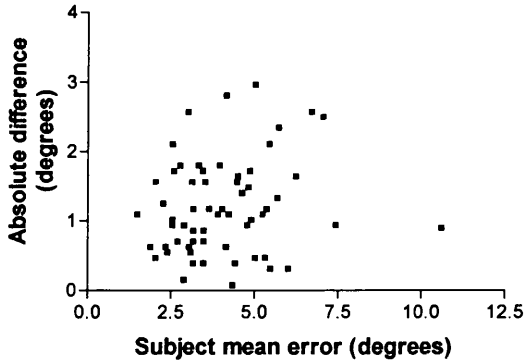

Figure 46 A plot showing the absolute difference in pointing responses between the first and second testing sessions versus the mean pointing error for individual subjects. Data is for all 20 control children, for all 3 pole locations, when viewing monocularly. Note that there is no correlation between the two (r=0.17, p=0.19).

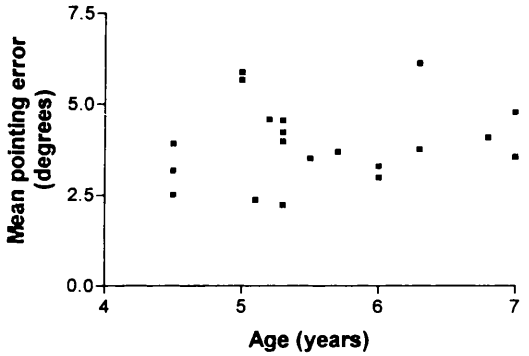

Figure 47 A plot showing the mean pointing errors versus age of individual subjects. Data is for all 20 control children when viewing monocularly and pooled for all 3 pole locations. Note that there is no correlation between the two (r=0.15, p=0.5).

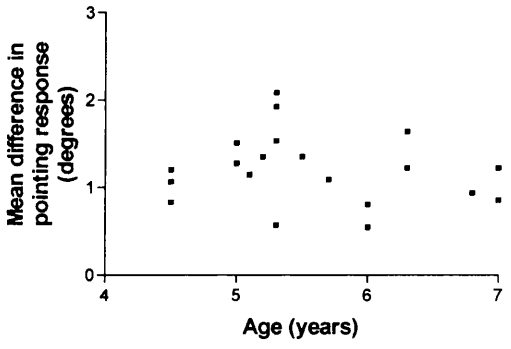

Figure 48 A plot showing the mean difference in pointing response between the first and second testing sessions versus age of individual subjects. Data is for all 20 control children when viewing monocularly and pooled for all 3 pole locations. Note that there is no correlation between the two (r=0.14, p=0.6)

8.2.3 DISCUSSION

These results show that the mean pointing errors are relatively high for all three poles, for both binocular and monocular viewing. This is not unexpected given the nature of the test, and in addition the young age of the children being tested. Pointing responses to the central pole were slightly more accurate than pointing responses to the eccentric poles in both viewing conditions, although these differences were not statistically significant. This pattern is similar to that described in previous studies [92, 93, 14, 45, 69]. Whilst there is an inherent variability in pointing responses between subjects the error appears to be consistent between repeated testing sessions. The coefficients of repeatability were 0.9 degrees and 1 degree, for binocular and monocular viewing respectively. We therefore expect, according to the British Standards Institution, 95% of differences of serial measurements in the same subject to be within 0.9 and 1 degree when viewing binocular and monocular respectively. This means that a difference in pointing response of greater than 0.9 – 1 degrees between testing sessions (depending on the viewing conditions) indicates at least a 95% chance of the change being real.

8.3 ASSESSMENT OF REPEATABILITY OF SPATIAL LOCALISATION IN ADULTS

8.3.1 METHODS

The method used to test spatial localisation in adult subjects was similar to that used in children (as described above), with the same equipment utilised. Ethical committee approval was obtained and all subjects gave informed consent.

Procedure

The following modifications were introduced when testing the adult subjects:

- Subjects were seated and viewed the computer touchscreen from a distance of 40cm.
- Pictures of three vertical poles were presented on the screen; in the centre,

and 15 degrees to the left and to the right of centre respectively (figure 49). The target used was a red 'ball' (1.8cm in diameter, luminance 45 cd/m^2), which was felt to be more appropriate for adults than a 'dragon'.

- Subjects were tested whilst viewing binocularly, and monocularly using both their right and left eyes.

The remainder of the testing procedure and data analysis was identical to that used in the children's study.

Subjects

20 subjects (10 male, 10 female) were tested and comprised members of staff of the Ophthalmology Department at Gartnavel General Hospital, as well as friends and relatives of the author. They had a mean age of 35 years and 6 months (SD 11 years; range 27 years to 65 years). Table 14 summarises these data. Inclusion criteria were the same as for the children's study. Visual acuities were recorded using logMAR crowded tests at a distance of 3 metres [79] and Curpax Test Type (Clement Clarke) at a distance of 25cm.

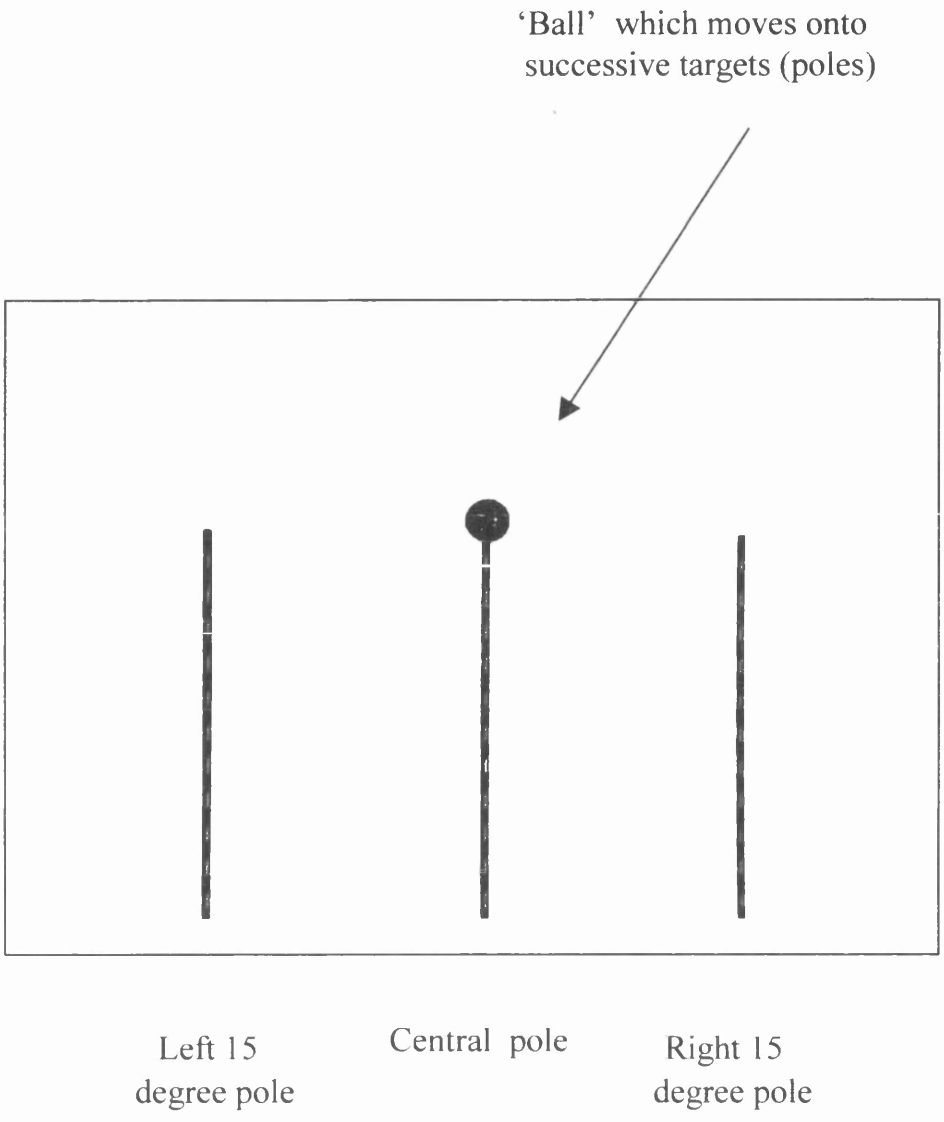

Figure 49 A diagram showing the computer touchscreen

Subject	Age	Distance acuity (LogMAR)		Near acuity		Refractive error (dioptres)	
		Right eye	Left eye	Right eye	Left eye	Right eye	Left eye
1	32	0	-0.1	N5	N5	-0.5	-0.5
2	46	-0.1	-0.05	N5	N5	0	0
3	31	-0.05	-0.025	N5	N5	-1	-0.75
4	30	-0.05	0.25	N5	N5	-2	-2
5	28	0	0.025	N5	N5	1	1.5
6	28	-0.075	-0.1	N5	N5	-3.25	-3.25
7	46	0	0	N5	N5	2	1.5
8	65	0	-0.1	N5	N5	2	2
9	36	-0.025	-0.075	N5	N5	-10	-9
10	65	-0.075	-0.025	N5	N5	2.5	3
11	29	-0.1	-0.075	N5	N5	0	0
12	31	-0.05	-0.025	N5	N5	-0.5	-0.25
13	30	-0.075	-0.1	N5	N5	0	0
14	30	-0.025	-0.05	N5	N5	-1	-1.75
15	39	-0.025	-0.025	N5	N5	-2.25	-2.75
16	28	-0.05	-0.05	N5	N5	-2.25	-1.75
17	27	-0.025	0	N5	N5	-2.5	-2.5
18	34	-0.05	-0.025	N5	N5	1.25	0.75
19	27	-0.025	-0.05	N5	N5	-0.75	-0.5
20	31	-0.025	-0.025	N5	N5	2.25	1.5

Table 14 Summary of details of the 20 control adults
Refractive errors represent mean spherical equivalents.

8.3.2 RESULTS

All of the subjects were able to perform the test without any difficulty. The mean distance visual acuity was –0.04 log units (SD 0.03) for the right eye and –0.03 (SD 0.08) log units for the left eye. The near visual acuity was N5 for both the right and left eyes for all subjects. Normality testing (Kolmogorov-Smirnov Test, Graph Pad Prism) confirmed a Gaussian distribution of the pointing responses, allowing parametric statistical tests to be performed on the data.

Binocular Results

Table 15 summarises the results for the adults when viewing binocularly. The overall mean pointing error for the two testing sessions was 2 degrees (SD 1.5). The overall mean difference in pointing response between the two sessions was 0.7 degrees (SD 0.35). The coefficient of repeatability for pointing response was 0.7 degrees. No relationship was found between differences in pointing response and pointing error for individual subjects ($r=0.08$, $p=0.6$; figure 50).

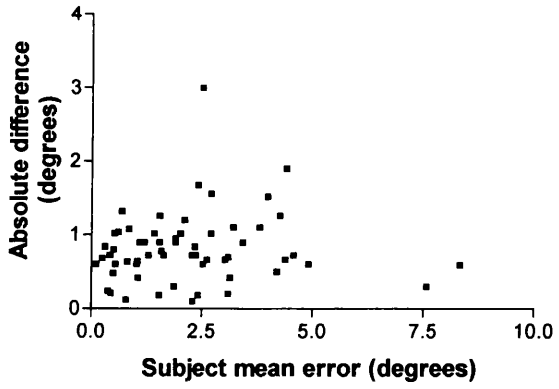

Figure 50 A plot showing the absolute difference in pointing responses between the first and second testing sessions versus the mean pointing error for individual subjects. Data is for all 20 control adults, for all 3 pole locations, when viewing binocularly. Note that there is no correlation between the two ($r=0.08$, $p=0.6$).

n = 20	Pole location			Overall
	Left 20°	Central	Right 20°	
Mean pointing error (1 + 2)	2.6	1.6	1.7	**2**
SD	2.2	1.1	1.4	**1.5**
95% Confidence Interval				**1.5-2.5**
Mean difference (1 - 2)	0.6	0.8	0.8	**0.7**
SD	0.3	0.4	0.3	**0.35**
95% Confidence Interval				**0.6-0.9**
Paired t test (comparing 1 with 2)	p=0.8	p=0.9	p=0.6	**p=0.8**
Coefficient of repeatability				**0.7**

Table 15 **The repeatability of pointing responses in 20 normal adults when viewing binocularly comparing the first (1) and second (2) testing sessions. All values represent degrees.**

Monocular Results

Tables 16 and 17 summarise the results for the adults when viewing monocularly with the right and left eyes respectively. When viewing with the right eye, the overall mean pointing error for the two testing sessions was 2.2 degrees (SD 1.5). The overall mean difference in pointing response between the two sessions was 0.8 degrees (SD 0.45). The coefficient of repeatability for pointing response was 0.9 degrees. No relationship was found between differences in pointing response and pointing error for individual subjects ($r=0.19$, $p=0.14$; figure 51). When viewing with the left eye, the overall mean pointing error for the two testing sessions was 2.7 degrees (SD 1.7). The overall mean difference in pointing response between the two sessions was 0.8 degrees (SD 0.4). The coefficient of repeatability for pointing response was 0.8 degrees. No relationship was found between differences in pointing response and pointing error for individual subjects ($r=0.04$, $p=0.7$; figure 52).

n=20	Pole location			Overall
	Left 20°	Central	Right 20°	
Mean pointing error (1 + 2)	2.3	1.9	2.6	**2.2**
SD	1.8	1.4	1.4	**1.5**
95% Confidence Interval				**1.8-2.6**
Mean difference (1 - 2)	0.7	0.9	0.9	**0.8**
SD	0.5	0.4	0.5	**0.45**
95% Confidence Interval				**0.5-1.0**
Paired t test (comparing 1 with 2)	p=0.8	p=0.6	p=0.4	**p=0.4**
Coefficient of repeatability				**0.9**

Table 16 The repeatability of pointing responses in 20 normal adults when viewing monocularly with the right eye, comparing the first (1) and second (2) testing sessions. All values represent degrees.

n=20	Pole location			Overall
	Left 20°	Central	Right 20°	
Mean pointing error (1 + 2)	3.2	2.5	2.5	**2.7**
SD	2.5	1	1.4	**1.7**
95% Confidence Interval				**2.1-3.4**
Mean difference (1 - 2)	0.6	1	0.8	**0.8**
SD	0.4	0.4	0.5	**0.4**
95% Confidence Interval				**0.6-1.0**
Paired t test (comparing 1 with 2)	p=0.7	p=0.8	p=0.8	**p=0.7**
Coefficient of repeatability				**0.8**

Table 17 The repeatability of pointing responses in 20 normal adults when viewing monocularly with the left eye, comparing the first (1) and second (2) testing sessions. All values represent degrees.

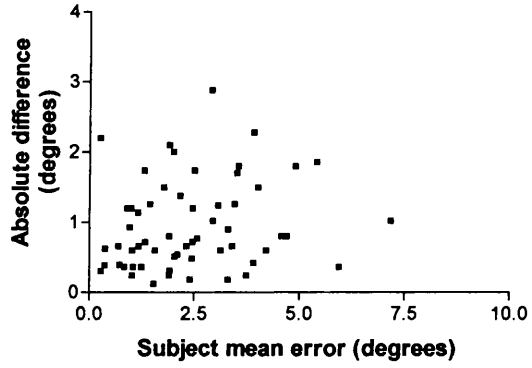

Figure 51 A plot showing the absolute difference in pointing responses between the first and second testing sessions versus the mean pointing error for individual subjects. Data is for all 20 control adults, for all 3 pole locations, when viewing monocularly with their right eye. Note that there is no correlation between the two (r=0.19, p=0.14).

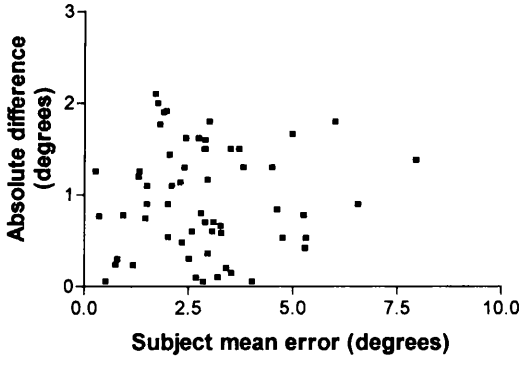

Figure 52 A plot showing the absolute difference in pointing responses between the first and second testing sessions versus the mean pointing error for individual subjects. Data is for all 20 control adults, for all 3 pole locations, when viewing monocularly with their left eye. Note that there is no correlation between the two (r=0.04, p=0.7).

8.3.3 DISCUSSION

As with the children's study the mean pointing errors are relatively high for all three poles for both binocular and monocular viewing, although not surprisingly they are lower than for children. Again the pointing responses to the central pole were slightly more accurate than pointing responses to the eccentric poles in both viewing conditions, although again this difference was not statistically significant. The coefficients of repeatability were 0.7, 0.9 and 0.8 degrees for binocular, right monocular and left monocular viewing respectively. We therefore expect 95% of differences of repeated measurements to be within 0.7 and 0.9 degrees when viewing binocular and monocular respectively. This means that a difference in pointing response of greater than 0.7 – 0.9 degrees (depending on the viewing conditions) between testing sessions indicates at least a 95% chance of the change being real.

8.4 CONCLUSION

The method described above is reliable for the repeated assessment of spatial localisation in the same individual (in both children and adults) and under different viewing conditions (i.e. binocularly and monocularly).

CHAPTER 9:
SPATIAL LOCALISATION IN FULLY ACCOMMODATIVE ESOTROPIA

9.1 INTRODUCTION

Spatial localisation is an essential part of normal visual function in both children and adults, and can be accurately assessed, as described in Chapter 8, by pointing to targets in surrounding space [77, 45, 48, 113]. Strabismic subjects are known to make errors when asked to perform such tasks of spatial localisation [77, 47, 45], particularly when they are unable to see their pointing hand (a procedure which eliminates visual feedback). However the aetiology of these errors is not fully understood. In addition, interpretation of the results of previous studies is hindered by the inclusion of subjects of varying age (both children and adults) and also with different types of strabismus (constant and intermittent esotropia and exotropia). Therefore, in this study it was decided to investigate spatial localisation in more detail in children of similar ages, with one specific form of strabismus, namely fully accommodative esotropia. This is a manifest convergent strabismus, caused by uncorrected hypermetropia and insufficient fusional divergence, in which full correction of the hypermetropic refractive error restores eye alignment [118]. This allows a comparison of the binocular pointing responses of these subjects when the eyes are aligned (when wearing glasses) and when there is a manifest squint (without glasses). A non-strabismic group of comparable hypermetropic subjects was also assessed.

9.2 METHODS

All procedures conformed to the Declaration of Helsinki for research involving human subjects. Ethical committee approval was obtained and parental informed consent was given in all cases.

9.2.1 Procedure

The testing procedure was very similar to that described for children in Chapter 8, the main difference being that each subject was tested both with and also without their hypermetropic refractive correction. To diminish any bias due to a

learning effect, a coin was tossed to determine which condition was tested first. All subjects were tested binocularly, with the hypermetropic, non-strabismic group also tested monocularly. Data analysis was also similar to that described in Chapter 8. The difference between the mean pointing errors 'with glasses' (not squinting) and 'without glasses' (squinting) was calculated for individual subjects for each pole. Statistical analysis was performed using GraphPad Prism.

9.2.2 Subjects

Ninety children participated in the study and were divided into three groups of 30 as follows:

1) right fully accommodative esotropia (mean age 5 years 9 months; range 4 years 4 months to 7 years).
2) left fully accommodative esotropia (mean age 5 years 11 months; range 4 years 5 months to 7 years 2 months).
3) hypermetropia (mean age 5 years 9 months; range 4 years 6 months to 7 years).

The number of subjects required in each group was determined using a power calculation (see Altman [4]). None of the children had a prior history of strabismus surgery and none had any past medical history of note. None of the fully accommodative subjects were aware of diplopia when their deviations were manifest. At the time of testing none had any evidence of amblyopia, as defined by a uniocular visual acuity of less than 0.250 (logMAR) or an interocular acuity difference of greater than 0.1 log units [106]. Visual acuities were recorded unaided and with refractive correction using logMAR crowded tests at a distance of 3 metres [79] and MacLure Reading Type for Children at a distance of 25cm. Where appropriate, the angles of the esodeviation for 6metres and 33cm, unaided and with refractive correction, were measured using the prism cover test. The strength of the spectacle correction worn was also noted. A summary of these clinical details is given in tables 18, 19 and 20 for the right fully accommodative, left fully accommodative and hypermetropic subjects respectively.

Subject	Age (years and months)	Refractive error (dioptres)		Angle of esodeviation (prism dioptres)	
		Right	Left	Near	Distance
1	5yrs 4 mths	5.25	4.50	16	12
2	6 yrs 2 mths	3.50	2.75	14	16
3	5 yrs 9 mths	3.25	3.00	30	25
4	5 yrs 6 mths	4.75	4.50	14	14
5	4 yrs 11 mths	7.75	7.75	35	30
6	6 yrs 2 mths	6.25	6.25	18	18
7	6 yrs 8 mths	5.25	4.75	30	18
8	6 yrs 9 mths	6.25	6.25	35	35
9	4 yrs 4 mths	7.75	7.75	30	20
10	5 yrs 6 mths	7.75	8.25	35	20
11	7 yrs	5.00	5.00	45	30
12	5 yrs 5 mths	5.75	5.75	25	18
13	6 yrs 10 mths	2.00	2.50	16	10
14	6 yrs 9 mths	4.75	4.50	50	45
15	5 yrs 8 mths	7.50	8.00	30	20
16	6 yrs	2.00	2.00	18	16
17	5 yrs 6 mths	5.50	5.50	16	14
18	5 yrs 7 mths	5.00	4.00	18	14
19	6 yrs	4.50	3.75	14	14
20	6 yrs 7 mths	5.00	5.50	30	25
21	6 yrs 3 mths	3.00	3.25	20	14
22	5 yrs	2.00	2.00	10	10
23	6 yrs	7.00	7.00	20	20
24	5 yrs 6 mths	5.75	5.25	30	16
25	6 yrs	7.00	6.00	30	25
26	6 yrs 3 mths	5.00	5.00	35	30
27	6 yrs	6.50	6.50	25	14
28	5 yrs 6 mths	5.05	5.50	16	14
29	6 yrs 6 mths	3.50	3.50	18	20
30	6 yrs 3 mths	6.50	6.25	25	20
Mean	5 yrs 9 mths	5.30	5.10	24.9	19.9
SD	7 mths	1.70	1.80	9.8	7.9

Table 18 Summary of clinical details of the right fully accommodative esotropic subjects. Refractive errors represent mean spherical equivalents (dioptres).

Subject	Age (years and months)	Refractive error (dioptres)		Angle of esodeviation (prism dioptres)	
		Right	Left	Near	Distance
1	6 yrs 3 months	6.25	6.75	45	35
2	5 yrs 3 mths	4.75	4.75	35	35
3	7 yrs	5.25	7.00	35	35
4	5 yrs 6 mths	3.75	4.25	20	20
5	7 yrs	4.00	4.75	30	20
6	7 yrs	5.00	6.00	40	30
7	4 yrs 6 mths	6.00	6.00	25	25
8	6 yrs 3 months	4.00	4.50	25	40
9	6 yrs	4.25	4.25	20	18
10	7 yrs	8.00	7.50	25	20
11	5 yrs	4.75	4.50	18	18
12	6 yrs 3 months	3.00	4.25	14	10
13	6 yrs 6 mths	4.75	6.00	35	30
14	5 yrs 6 mths	5.00	5.00	14	10
15	4 yrs 5 mths	4.75	5.50	30	25
16	4 yrs 9 mths	2.00	4.75	25	20
17	6 yrs	4.00	4.00	35	30
18	6 yrs 6 mths	5.25	5.75	20	20
19	5 yrs 3 mths	4.00	5.00	35	30
20	5 yrs 4 mths	7.50	7.75	30	30
21	6 yrs	5.75	6.00	65	50
22	6 yrs 6 mths	5.25	5.75	35	30
23	5 yrs	2.50	2.50	12	16
24	5 yrs 6 mths	6.75	6.75	40	25
25	6 yrs 9 mths	6.00	6.00	30	25
26	7 yrs	6.25	6.50	20	20
27	5 yrs	4.75	5.25	30	25
28	5 yrs 5 mths	2.25	4.00	35	30
29	6 yrs 1 mth	3.50	3.75	25	20
30	6 yrs 6 mths	2.00	2.75	30	20
Mean	**5 years 11 months**	**4.70**	**5.25**	**29.2**	**25.4**
SD	**9 months**	**1.50**	**1.30**	**10.9**	**8.8**

Table 19 Summary of clinical details of the left fully accommodative esotropic subjects. Refractive errors represent mean spherical equivalents (dioptres).

Subject	Age (years and months)	Refractive error (dioptres)	
		Right	Left
1	6 yrs 2 mths	4.50	3.75
2	5 yrs	3.75	4.25
3	5 yrs	5.50	5.75
4	6 yrs	5.75	6.75
5	5 yrs 6 mths	2.50	3.00
6	6 yrs	2.50	2.75
7	5 yrs 6 mths	2.50	2.75
8	7 yrs	4.75	5.00
9	6 yrs	2.50	2.50
10	5 yrs 4 mths	2.75	2.50
11	6 yrs 6 mths	4.75	4.75
12	6 yrs	6.625	6.00
13	4 yrs 6 mths	4.00	5.00
14	6 yrs	3.625	2.5
15	6 yrs	3.00	3.00
16	4 yrs 6 mths	2.50	2.25
17	7 yrs	2.50	2.50
18	6 yrs	3.25	2.50
19	5 yrs	4.00	4.50
20	5 yrs 10 mths	4.375	4.375
21	6 yrs 5 mths	2.50	3.50
22	5 yrs 7 mths	2.75	2.50
23	5 yrs	3.375	3.50
24	6 yrs 1 mth	4.75	5.00
25	6 yrs 6 mths	2.50	2.50
26	6 yrs	5.50	4.50
27	6 yrs 4 mths	4.00	4.50
28	5 yrs	3.25	3.00
29	7 yrs	5.00	4.75
30	6 yrs 1 mth	7.25	7.00
Mean	**5 yrs 9 mths**	**3.90**	**4.00**
SD	**8 mths**	**1.3**	**1.4**

Table 20 Summary of clinical details of the hypermetropic subjects. Refractive errors represent mean spherical equivalents (dioptres).

9.3 RESULTS

All of the children were able to perform the test without any difficulty, both with and without spectacle correction. Normality testing (Kolmogorov-Smirnov Test, Graph Pad Prism) confirmed a Gaussian distribution of the data, allowing parametric statistical tests to be performed.

For children with right fully accommodative esotropia, the mean decrease in distance visual acuity when not wearing spectacle correction was 0.14 log units (SD 0.1) for the right eye and 0.1 log units (SD 0.08) for the left eye. For children with left fully accommodative esotropia, the mean decrease in distance visual acuity when not wearing spectacle correction was 0.1 log units (SD 0.1) for the right eye and 0.13 log units (SD 0.07) for the left eye. For hypermetropic children the mean decrease in visual acuity when not wearing spectacle correction was 0.1 log units (SD 0.09) for both eyes. Near visual acuity was N5 in all of the fully accommodative and hypermetropic subjects with and without spectacle correction. Tables 21, 22 and 23 summarise these data.

Subject	Corrected Visual Acuities				Uncorrected Visual Acuities			
	Distance		Near		Distance		Near	
	Right	Left	Right	Left	Right	Left	Right	Left
1	0.1	0.025	N5	N5	0.15	0.05	N5	N5
2	0.075	0	N5	N5	0.225	0.075	N5	N5
3	0.15	0.15	N5	N5	0.25	0.25	N5	N5
4	0.05	0	N5	N5	0.2	0.1	N5	N5
5	0.05	-0.025	N5	N5	0.2	0.25	N5	N5
6	0.025	0	N5	N5	0.15	0.1	N5	N5
7	0.15	0	N5	N5	0.35	0.1	N5	N5
8	0.075	0.1	N5	N5	0.2	0.25	N5	N5
9	0.15	0.15	N5	N5	0.35	0.25	N5	N5
10	0.125	0.075	N5	N5	0.25	0.2	N5	N5
11	0.05	0.125	N5	N5	0.15	0.2	N5	N5
12	0.15	0.1	N5	N5	0.3	0.15	N5	N5
13	0.175	0.05	N5	N5	0.3	0.1	N5	N5
14	0.05	0	N5	N5	0.15	0.025	N5	N5
15	0.375	0.375	N5	N5	0.525	0.5	N5	N5
16	0.1	0.025	N5	N5	0.1	0.125	N5	N5
17	0.15	0.1	N5	N5	0.35	0.25	N5	N5
18	0.175	0.1	N5	N5	0.3	0.15	N5	N5
19	0.025	0.025	N5	N5	0.15	0.075	N5	N5
20	0.25	0.3	N5	N5	0.375	0.175	N5	N5
21	0.05	0	N5	N5	0.2	0.1	N5	N5
22	0.05	0.05	N5	N5	0.1	0.125	N5	N5
23	0.325	0.2	N5	N5	0.45	0.375	N5	N5
24	0.125	0.075	N5	N5	0.4	0.35	N5	N5
25	0.2	0.1	N5	N5	0.475	0.2	N5	N5
26	0.2	0.2	N5	N5	0.25	0.25	N5	N5
27	0.1	0.025	N5	N5	0.175	0.125	N5	N5
28	0.15	0.1	N5	N5	0.55	0.25	N5	N5
29	0	0.025	N5	N5	0.025	0.025	N5	N5
30	0.15	0.175	N5	N5	0.4	0.375	N5	N5
Mean	**0.13**	**0.09**	**N5**	**N5**	**0.27**	**0.19**	**N5**	**N5**
SD	**0.09**	**0.09**			**0.13**	**0.11**		

Table 21 Summary of visual acuities of the right fully accommodative esotropic subject Distance acuities represent LogMAR.

Subject	Corrected Visual Acuities				Uncorrected Visual Acuities			
	Distance		Near		Distance		Near	
	Right	Left	Right	Left	Right	Left	Right	Left
1	0.125	0.2	N5	N5	0.25	0.4	N5	N5
2	0.075	0.125	N5	N5	0.15	0.25	N5	N5
3	0.05	0.2	N5	N5	0.125	0.35	N5	N5
4	0.075	0.1	N5	N5	0.125	0.25	N5	N5
5	0.175	0.175	N5	N5	0.25	0.3	N5	N5
6	0.1	0.1	N5	N5	0.15	0.25	N5	N5
7	0.25	0.25	N5	N5	0.35	0.375	N5	N5
8	0.1	0.2	N5	N5	0.15	0.325	N5	N5
9	0	0.025	N5	N5	0.075	0.175	N5	N5
10	0.1	0.125	N5	N5	0.475	0.35	N5	N5
11	0.1	0.2	N5	N5	0.2	0.3	N5	N5
12	0.075	0.125	N5	N5	0.075	0.225	N5	N5
13	0.05	0.1	N5	N5	0.05	0.125	N5	N5
14	0.025	0.125	N5	N5	0.15	0.225	N5	N5
15	0.2	0.3	N5	N5	0.3	0.45	N5	N5
16	-0.025	0.05	N5	N5	0.025	0.125	N5	N5
17	0.2	0.3	N5	N5	0.6	0.45	N5	N5
18	0.025	0.125	N5	N5	0.05	0.25	N5	N5
19	0.125	0.225	N5	N5	0.2	0.45	N5	N5
20	0.125	0.175	N5	N5	0.35	0.35	N5	N5
21	0.025	0.025	N5	N5	0.375	0.375	N5	N5
22	0.1	0.15	N5	N5	0.175	0.35	N5	N5
23	0.05	0.1	N5	N5	0.1	0.2	N5	N5
24	0.175	0.1	N5	N5	0.35	0.225	N5	N5
25	0.25	0.175	N5	N5	0.25	0.2	N5	N5
26	0.3	0.3	N5	N5	0.425	0.45	N5	N5
27	0.1	0.15	N5	N5	0.2	0.3	N5	N5
28	0	0.1	N5	N5	0.075	0.3	N5	N5
29	0.075	0.075	N5	N5	0.075	0.1	N5	N5
30	0.025	0.025	N5	N5	0.05	0.125	N5	N5
Mean	**0.1**	**0.15**	**N5**	**N5**	**0.21**	**0.29**	**N5**	**N5**
SD	**0.08**	**0.08**			**0.15**	**0.1**		

Table 22 Summary of visual acuities of the left fully accommodative esotropic subjects Distance acuities represent LogMAR.

Subject	Corrected Visual Acuities				Uncorrected Visual Acuities			
	Distance		Near		Distance		Near	
	Right	Left	Right	Left	Right	Left	Right	Left
1	0.175	0.125	N5	N5	0.275	0.225	N5	N5
2	0.175	0.15	N5	N5	0.25	0.2	N5	N5
3	0.075	0.1	N5	N5	0.325	0.325	N5	N5
4	0.05	0.075	N5	N5	0.175	0.2	N5	N5
5	0.05	0.1	N5	N5	0.125	0.15	N5	N5
6	0.075	0.05	N5	N5	0.225	0.175	N5	N5
7	0.025	0.025	N5	N5	0.075	0.1	N5	N5
8	0.075	0.075	N5	N5	0.125	0.15	N5	N5
9	0.025	0.025	N5	N5	0.025	0.05	N5	N5
10	0.175	0.125	N5	N5	0.25	0.2	N5	N5
11	0.225	0.15	N5	N5	0.325	0.275	N5	N5
12	0.05	0	N5	N5	0.225	0.175	N5	N5
13	0	0.125	N5	N5	0	0.15	N5	N5
14	0.15	0.075	N5	N5	0.2	0.2	N5	N5
15	0.025	0.025	N5	N5	0.025	0.05	N5	N5
16	0.05	0.025	N5	N5	0.15	0.025	N5	N5
17	0.025	0.025	N5	N5	0.1	0.075	N5	N5
18	0.05	0	N5	N5	0.125	0	N5	N5
19	0.05	0.125	N5	N5	0.1	0.275	N5	N5
20	0.125	0.15	N5	N5	0.225	0.275	N5	N5
21	0	0.05	N5	N5	0.025	0.25	N5	N5
22	0	0.025	N5	N5	0.1	0.1	N5	N5
23	0	0.025	N5	N5	0.125	0.125	N5	N5
24	0.05	0.075	N5	N5	0.275	0.2	N5	N5
25	0.075	0.1	N5	N5	0.075	0.1	N5	N5
26	0.125	0.1	N5	N5	0.6	0.525	N5	N5
27	0.125	0.1	N5	N5	0.2	0.1	N5	N5
28	-0.05	-0.1	N5	N5	0.1	0.05	N5	N5
29	0.125	0.025	N5	N5	0.175	0.15	N5	N5
30	0.225	0.225	N5	N5	0.325	0.35	N5	N5
Mean	**0.08**	**0.07**	**N5**	**N5**	**0.18**	**0.17**	**N5**	**N5**
SD	**0.07**	**0.06**			**0.12**	**0.12**		

Table 23 Summary of visual acuities of the hypermetropic subjects. Distance acuities represent LogMAR.

A significant shift in the mean pointing response to the central target was found in both the left and right fully accommodative groups when comparing 'with glasses' (not squinting) to 'without glasses' (squinting). This is shown in figure 53. The right fully accommodative esotropes showed a mean pointing shift to the left of 1.7 degrees (SD 2.1) when they were squinting (paired t test, $p<0.001$, $t=5.1$). This effect was observed in 24 (80%) subjects. The left fully accommodative esotropes showed a mean pointing shift to the right of 1.1 degrees (SD 1.2) when they were squinting (paired t test, $p<0.001$, $t=4.96$). This effect was observed in 25 (83%) subjects. There was no significant shift in the localisation position for the two eccentric targets in either strabismic group when they were tested without glasses. For example, for the left 20 degree target, the right fully accommodative esotropes showed a mean pointing shift to the left of 0.3 degrees (SD 2.6; $p=0.5$, $t=0.6$) and the left fully accommodative esotropes showed a mean shift of 0.4 degrees to the right (SD 2.9; $p=0.5$, $t=0.7$). This is shown in figure 54. For the right 20 degree target, the right fully accommodative esotropes showed a mean pointing shift to the left of 0.1 degrees (SD 3.0; $p=0.8$, $t=0.2$) and the left fully accommodative esotropes showed a mean shift of 0.2 degrees to the right (SD 2.7; $p=0.6$, $t=0.5$). This is shown in figure 55.

No significant localisation shift was observed in the hypermetropic group for any of the three targets when they were tested binocularly without their glasses (figures 53 - 55). For example, for the left eccentric, centre and right eccentric targets they showed a mean shift of 0.2 degrees to the right (SD 3.3; paired t test, $p=0.7$, $t=0.4$), 0.2 degrees to the left (SD 2.6; $p=0.7$, $t=0.4$) and 0.4 degrees to the right (SD 3.0; $p=0.5$, $t=0.7$) respectively. In addition, no significant localisation shift was observed in the hypermetropic group for any of the three targets when they were tested monocularly without their glasses (figure 56). For example, for the left eccentric, centre and right eccentric targets they showed a mean shift of 0.1 degrees to the left (SD 3.5; paired t test, $p=0.9$, $t=0.1$), 0.2 degrees to the right (SD 2.9; $p=0.8$, $t=0.3$) and 0.4 degrees to the left (SD 3.6; $p=0.3$, $t=1$) respectively.

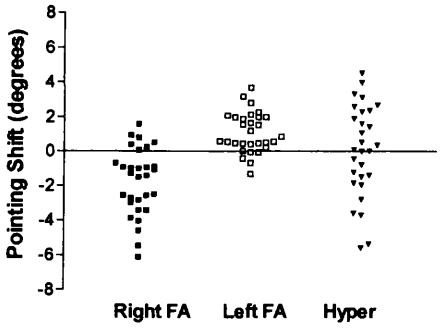

Figure 53 Mean horizontal pointing shifts for individual strabismic and hypermetropic subjects for the central target.

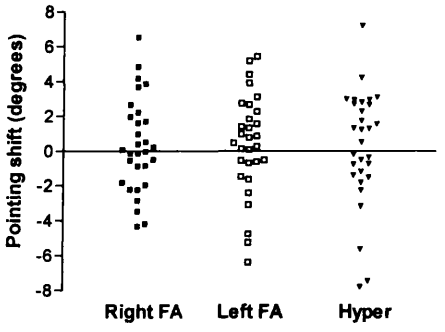

Figure 54 Mean horizontal pointing shifts for individual strabismic and hypermetropic subjects for the left 20 degree eccentric target.

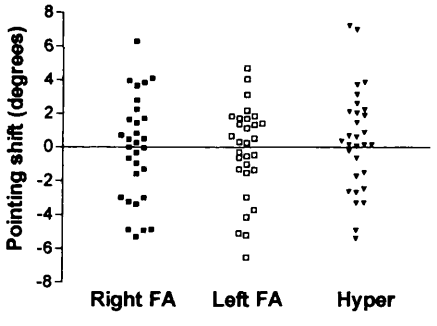

Figure 55 Mean horizontal pointing shifts for individual strabismic and hypermetropic subjects for the right 20 degree eccentric target.

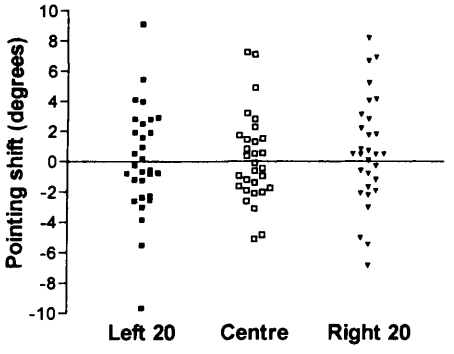

Figure 56 Mean horizontal pointing shifts for individual hypermetropic subjects for all 3 target locations when tested monocularly without their glasses.

Figures 53 - 56 Mean horizontal pointing shifts for individual subjects for the central and and eccentric targets. Positive values represent shifts to the right and negative values represent shifts to the left.
Right FA = right fully accommodative esotropes.
Left FA = left fully accommodative esotropes.
Hyper = non-strabismic hypermetropes.
n=30 for each group of subjects.

For the strabismic groups, no correlation was found between refractive error, the age of the subjects, the angle of the deviation and pointing shift (figures 57 -60).

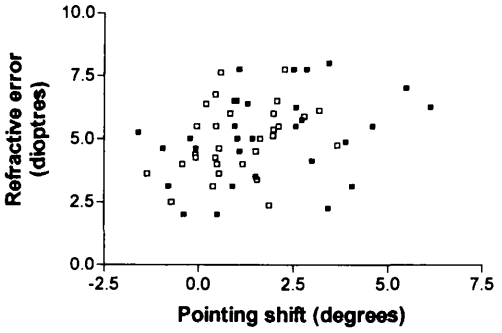

Figure 57 A plot showing the mean pointing shifts of individual strabismic subjects versus their refractive error (mean spherical equivalent for both eyes).
Note that there is no correlation between these variables (r=0.3, p=0.1; and r=0.31, p=0.09 for right and left fully accommodative subjects respectively).

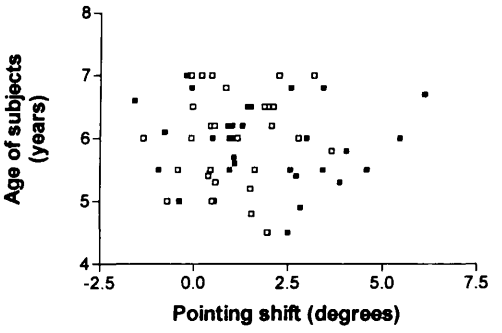

Figure 58 A plot showing the mean pointing shifts of individual strabismic subjects versus their age.
Note that there is no correlation between these variables (r=0.13, p=0.5; and r=0.06. p=0.76 for right and left fully accommodative subjects respectively).

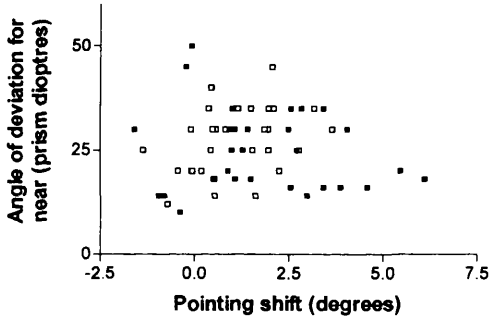

Figure 59 A plot showing the mean pointing shifts of individual strabismic subjects versus their angle of deviation for near.
Note that there is no correlation between these variables (r=0.17, p=0.36; and r=0.3, p=0.08 for right and left fully accommodative subjects respectively).

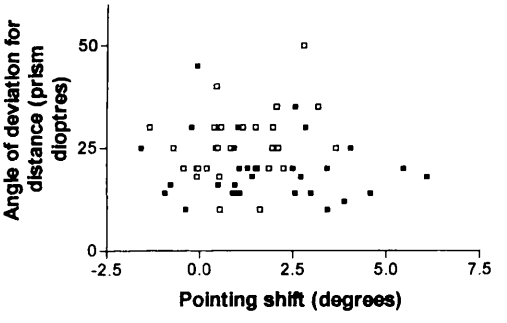

Figure 60 A plot showing the mean pointing shifts of individual strabismic subjects versus their angle of deviation for distance.
Note that there is no correlation between these variables (r=0.14, p=0.45; and r=0.26. p=0.16 for right and left fully accommodative subjects respectively).

Figures 57 - 60 Plots showing the relationships between mean pointing shifts for individual subjects and their refractive error, age and angles of deviation.
Filled and open symbols represent right and left fully accommodative subjects respectively. n=30 for each group of subjects.

9.4 DISCUSSION

This study demonstrates that for centrally located targets, spatial localisation in children with fully accommodative esotropia shifts in the direction of the non-squinting eye when the deviation is manifest. Changes in spatial localisation in this well-defined group of strabismic subjects have not been reported previously. Assessing pointing responses without being able to see the pointing hand is a recognised method of assessing the accuracy of spatial localisation in both children and adults [113, 48, 45]. The variability of responses observed in this study is not surprising considering that the mean age of the children being tested was less than 6 years of age and that such studies by their very nature (i.e. pointing without being able to see the hand) tend to be variable.

The shift in pointing response was only observed for the central target. A small effect may have been present at the eccentric positions but could have be masked by the greater variability of the pointing responses, as noted by the larger standard deviations. In addition, it is conceivable that peripherally located targets could have stimulated retinal loci outwith the suppression scotomas in the deviating eye. This would have provided further visual information that would help determine the altered direction of gaze of the squinting eye, thereby preventing a localisation shift. Interestingly, Fronius & Sireteanu [45] tested the pointing responses in a heterogeneous group of strabismic subjects and concluded that spatial localisation may be altered to varying degrees within different areas of the visual field. Although they only assessed four patients under similar experimental conditions to this study (i.e. unable to see their pointing hand) their results do highlight the variable nature of spatial localisation, particularly amongst strabismic patients.

For the central target, the direction of the pointing shift was noted to be in the direction in which the squinting eye was looking. The fact that the position of one (presumably suppressed) eye can influence the perception of visual direction when viewing with the dominant, contralateral eye is not surprising. When Ono and Weber [87] studied the pointing responses of normal adult subjects they found that during monocular viewing, a shift in spatial localisation occurred. The direction of this shift was related to the direction of the phoria of the occluded eye, indicating that the position of both eyes is taken into account

when performing such tasks. A similar finding was reported by Mann et. al. [77], who studied a group of constantly suppressing esotropic and exotropic strabismic patients. They noted that positional information from the dominant eye influenced the pointing responses when subjects viewed targets monocularly with their suppressed eye. They also found that the size of the localisation shift correlated with the angle of strabismus. However, this study failed to identify such a relationship, a result that is in keeping with Fronius & Sireteanu [45], who emphasise that this lack of correlation is not unexpected given the complex aetiology of pointing errors in strabismic subjects. While there are similarities between this study and those of Mann et. al. [77] and Fronius & Sireteanu [45], it should be remembered that their studies examined monocular spatial localisation, in contrast to our binocular testing procedure, which is perhaps more relevant to everyday tasks. In addition, their subjects were significantly older (aged from 6 years to 32 years) and had several different types of strabismus (including both esotropia and exotropia). In contrast, this study assessed younger children (aged from 4 years 6 months to 7 years) who were all fully accommodative esotropes.

Why should a shift in the pointing response be observed when the children are squinting? As was discussed in the introduction we rely on a combination of both retinal and extraretinal information for accurate spatial localisation. Therefore a change in one of these might account for our findings and this will be discussed in more detail below. This assumes of course, that the localisation shifts that were observed were not related to any alteration in the motor control of the pointing arm. There is no reason to believe otherwise.

Change in retinal (visual) information:

The fully accommodative subjects' distance visual acuities dropped when they removed their glasses. It is possible that this resulted in a greater degree of inaccuracy when performing the pointing test, and might, therefore, explain our findings. This, however, is unlikely, because the hypermetropic control group also had a similar reduction in their distance acuities, but showed no significant change in pointing response when they were tested without their refractive

correction. Although the drop in distance acuity was greater for the deviating eye, this is unlikely to have been a contributory factor as none of the subjects complained of diplopia. It was assumed, therefore, that the retinal image from this eye was suppressed and did not provide visual information about the location of the central target. In addition, the testing was performed at a distance of 26.5cm (i.e. near), and in both the fully accommodative groups, near vision remained at N5 in all subjects.

Another aspect of visual function, which changed when the children were squinting, was binocularity; when their deviation is manifest they no longer have stereopsis. Could this have affected their spatial perception? Again this is unlikely because when the hypermetropic group were tested monocularly (thereby eliminating binocular vision), it did not affect their perceived location of the target. On this basis it can be assumed that stereopsis is not required to perform the test accurately.

Change in extraretinal information:

If visual (retinal) information cannot explain the pointing shift, then a change in the nature of the extraretinal eye position signal that is used to determine visual direction might be the answer. As discussed above, the two possible sources of this extraretinal information are efference copy and extraocular muscle proprioception.

Could the efferent copy of the oculomotor command change when the children are squinting? When their deviations are manifest the fixating, dominant eye, views the same targets in the same position as when their eyes are aligned. According to Walls [119] the visual system only monitors the efference command sent to the dominant eye. If this is the case in our subjects with fully accommodative esotropia, then efference copy should be unchanged when the non-dominant eye is squinting. This means that the shift in localisation that was observed cannot be explained by an alteration in efference copy. Bridgeman [16] also supports the notion that there is only one copy of the efferent command, which, according to Hering's law, represents the equal motor innervation sent to both eyes. Whilst this would be sufficient to specify binocular visual direction when the eyes are aligned, it is not clear what happens to efference copy when

one eye is deviated relative to the other. In view of this there must be a degree of uncertainty about the role of efference copy in manifest strabismus and whether it influences the extraretinal eye position signal that contributes to spatial localisation under such circumstances.

The second component of extraretinal eye position information is proprioceptive input from the extraocular muscles. In our strabismic subjects, when their deviation is manifest, the relative stretch on the lateral rectus and medial rectus muscles of the squinting eye must be different to that of the fixing, non-squinting eye. It is reasonable to assume, therefore, that the proprioceptive feedback must be altered. As the sense of visual direction is partly determined by the afferent input from both eyes, this could result in an erroneous eye position signal, producing a shift in the perceived location of a target. There is an increasing body of evidence to support such an explanation. For example, Gauthier et al [48] created an 'experimental strabismus' in normal subjects by passively rotating one eye using a suction contact lens, a technique believed to modify extraocular muscle proprioception. When this was done, the subjects consistently mislocated targets in the direction of the deviation, a finding consistent with the results of this study. Other experimental studies [116, 55] have demonstrated that manipulating extraocular muscle proprioception produces mean pointing shifts of 2.5 and 2.98 degrees respectively. Although these shifts are slightly larger than those described in this study, they are of a similar magnitude. Alterations in pointing responses following different forms of strabismus surgery have also been reported [113, 112], findings believed to result from modified proprioception secondary to surgical damage. The exact site(s) at which proprioception influences spatial perception is not known, although possibilities include the lateral geniculate nucleus and the visual cortex, both of which respond to stimulation of extraocular muscle afferent input [20, 41].

Whilst the localisation shifts that have been observed are likely to be the result of a change in the extraretinal eye position signal, it is not known if this is due to an alteration in efference copy, proprioception or both. However, the balance of evidence certainly suggests that modified proprioception is a contributory factor.

CHAPTER 10:
THE EFFECT OF RETINAL DETACHMENT SURGERY ON SPATIAL LOCALISATION

10.1 INTRODUCTION

Not only does spatial localisation alter in strabismic children under certain conditions, as described in Chapter 9, but strabismus surgery can also produce shifts as a probable consequence of modified afferent input from the extraocular muscles [113, 112]. This is discussed in detail in Chapter 3. Other forms of surgery are reported to affect the perception of target location. For example, patients undergoing conventional scleral buckling surgery for retinal detachment have been shown to make errors when asked to perform tasks of spatial localisation, whilst viewing targets with the operated eye [23]. These changes were attributed to alterations in extraocular muscle proprioception, as a consequence of the perioperative manipulation of the muscles. However, the visual information available to these patients in the immediate post-operative period (i.e. acuity and field of vision) must also have altered. This is likely to have contributed more to these errors than the change in proprioception.

It was of interest to note that post-operative localisation shifts were found in 4 out of 10 of these patients when they were tested whilst viewing with the fellow unoperated eye. It is reasonable to assume that under these circumstances, modified extraocular muscle afferent feedback from the operated eye influenced the central interpretation of gaze direction, particularly as it is known that eye position information from both eyes is utilised for this very purpose [77, 87]. If this were the case then patients undergoing retinal detachment surgery, which does not directly involve manipulating the extraocular muscles (i.e. vitrectomy) would not be expected to demonstrate any localisation changes post-operatively when viewing with the fellow unoperated eye. To test this hypothesis a comparison of the effect on spatial localisation of 2 different surgical procedures for primary rhegmatogenous retinal detachment, namely conventional external scleral buckling, and vitrectomy, was made.

10.2 METHODS

All procedures conformed to the Declaration of Helsinki for research involving human subjects. Ethical committee approval was obtained and informed consent was given in all cases.

10.2.1 Protocol

This was a non-randomised prospective study. The testing protocol was very similar to that described for adults in Chapter 8, the main difference being that each subject was tested prior to surgery (either the day before, or the day of surgery) and then on the first post-operative day. A further test was carried out on the first follow-up visit, approximately 10 days later. All subjects were tested with appropriate refractive correction whilst viewing monocularly with the unoperated eye, the operated eye being patched during this time. Data analysis was also similar to that described in Chapter 8. The differences between the mean pointing errors recorded pre-operatively, on the first post-operative day and at the subsequent follow up visit were then calculated for individual subjects for each pole. Statistical analysis was performed using GraphPad Prism.

10.2.2 Subjects

Sixty patients who underwent surgery for primary rhegmatogenous retinal detachment participated in the study and were divided into two groups of 30 as follows:

1) those who underwent primary external scleral buckling (mean age 48 years, SD 17, range 19 years to 83 years).
2) those who underwent primary vitrectomy (mean age 55 years, SD 15, range 23 years to 73 years).

The choice of surgical procedure to be performed was determined by one of the vitreo-retinal surgeons (HH, TB or JM) and was dependent upon the requirements of individual patients.

The number of subjects required in each group was determined using a power calculation (see Altman[4]). None of the subjects had any previous ophthalmic history of note and no prior medical history that could have affected their ocular

motility or pointing responses. Visual acuities were recorded with appropriate refractive correction using the logMAR crowded test at a distance of 3 metres [79]. A summary of these clinical details is given in Tables 24, 25 and 26.

10.2.3 Surgical Procedure

All surgery was performed under general anaesthesia. The conventional external scleral buckling procedures consisted of drainage of subretinal fluid and application of cryotherapy in the region of the retinal break(s) to create an adhesion between the sensory retina and the underlying retinal pigment epithelium. Silicone explants were placed overlying the retinal break(s) and orientated either circumferentially (n=25) or radially (n=5). An encircling band was also used where appropriate (n=12). Intravitreal gas was used to effect temporary internal tamponade as required. All four of the rectus muscles were slung to aid movement of the eye. The vitrectomy procedures consisted of a standard three-port pars plana approach, with internal drainage of subretinal fluid, followed by fluid/gas exchange. External cryotherapy was applied in the region of the retinal hole(s). No muscle slings or external buckles were used in the vitrectomy group.

Subject	Age (years)	Affected Eye	Macula status	Visual acuity (log units)		Refractive error (dioptres)	
				Right	Left	Right	Left
1	32	Right	Attached	0.025	-0.1	-5.00	-4.00
2	30	Left	Attached	-0.1	0.1	-3.75	-3.50
3	31	Right	Detached	HM	-0.075	0	0
4	57	Right	Attached	0.3	0.1	2.00	2.50
5	58	Left	Attached	-0.05	0.35	-6.50	-7.00
6	40	Left	Detached	0	0.8	0	0
7	63	Right	Attached	0.1	-0.025	3.50	3.00
8	64	Left	Detached	0.125	HM	2.00	2.00
9	41	Right	Attached	0.225	0.075	-5.5	-5.75
10	46	Right	Detached	0.4	-0.025	-2.50	-2.50
11	83	Left	Attached	0.075	0.175	-0.50	-0.50
12	37	Right	Detached	0.8	-0.05	-0.50	-0.50
13	43	Left	Attached	-0.05	0.125	-8.50	-7.50
14	44	Right	Detached	0.8	-0.075	-2.50	-2.50
15	20	Left	Detached	-0.1	0.8	-4.00	-4.75
16	57	Right	Attached	0.225	0.175	-6.25	-7.25
17	72	Right	Detached	CF	0.05	-5.00	-5.00
18	47	Left	Attached	-0.125	0.3	-2.25	-2.00
19	62	Left	Detached	0.075	HM	-4.50	-5.00
20	40	Right	Detached	HM	-0.075	-10.00	-9.25
21	46	Left	Detached	0.075	HM	0	0
22	79	Right	Detached	HM	-0.05	-8.00	-7.00
23	76	Left	Detached	0.1	HM	-4.00	-3.00
24	50	Right	Attached	0.225	-0.075	-5.00	-6.50
25	46	Left	Attached	-0.025	0.325	-3.00	-2.50
26	26	Right	Attached	0.4	0	-0.50	-0.50
27	19	Right	Detached	0.8	-0.075	-6.00	-7.00
28	45	Left	Attached	-0.075	0.25	-9.75	-6.75
29	27	Right	Detached	0.35	0	-4.00	-3.50
30	45	Left	Detached	0.6	-0.025	-3.50	-3.25
Mean	**48**					**-3.44**	**-3.32**
SD	**17**					**3.5**	**3.3**

Table 24. Summary of the clinical details for the scleral buckling group. Refractive errors represent mean spherical equivalents. Acuities represent LogMAR where possible; CF = counting fingers, HM = hand movements.

Subject	Age (years)	Affected Eye	Macula status	Visual acuity (log units)		Refractive error (dioptres)	
				Right	Left	Right	Left
1	72	Right	Detached	POL	-0.025	-2.50	-2.75
2	48	Right	Detached	0.8	0.15	-6.00	-5.75
3	23	Right	Detached	POL	-0.05	0	0
4	74	Left	Detached	0.05	POL	2.00	2.00
5	70	Left	Detached	0.15	HM	-4.50	-5.25
6	70	Left	Attached	0.025	0.6	-2.00	-2.50
7	45	Left	Detached	0.025	CF	-1.25	-1.50
8	68	Right	Detached	CF	0	-7.00	-8.00
9	65	Right	Detached	CF	0.1	-5.00	-3.00
10	50	Right	Attached	0.25	0.025	2.00	3.00
11	59	Left	Detached	0.1	CF	-4.50	-5.00
12	44	Right	Detached	HM	-0.075	-2.50	-2.00
13	59	Right	Detached	CF	0.2	-15.00	-14.00
14	62	Left	Detached	0.15	HM	1.00	-1.00
15	71	Right	Detached	0.8	0.075	-9.00	-6.00
16	62	Right	Detached	0.7	0.125	-3.00	-3.00
17	27	Left	Attached	0.025	HM	-2.00	-6.00
18	49	Right	Detached	0.8	-0.1	1.50	1.50
19	59	Left	Attached	0.025	0.15	0.25	-0.25
20	68	Right	Detached	HM	0.05	4.00	3.00
21	46	Right	Detached	HM	0.225	-4.00	-3.00
22	71	Right	Detached	0.8	0.025	3.25	3.50
23	34	Left	Attached	0.425	CF	-13.75	-13.5
24	54	Left	Detached	-0.075	HM	-1.00	-1.00
25	60	Right	Attached	0.525	-0.025	-6.00	-5.75
26	64	Right	Detached	0.8	-0.075	0	-1.00
27	28	Left	Detached	-0.125	POL	0	0
28	73	Left	Detached	0.025	HM	-4.50	-3.75
29	49	Right	Detached	HM	-0.05	-5.00	-4.00
30	40	Left	Attached	0.025	0.2	-3.00	-3.25
Mean	**55**					**-2.91**	**-2.93**
SD	**15**					**4.5**	**4.2**

Table 25. Summary of the clinical details for the vitrectomy group. Refractive errors represent mean spherical equivalents. Acuities represent LogMAR where possible; CF = counting fingers, HM = hand movements, POL = perception of light.

		Scleral buckling	Vitrectomy
Pre-operative :	Operated eye	0.025 - HM	0.15 - PoL
	Fellow eye	0.02 (0.09)	0.04 (0.11)
Day 1 Post-op :	Operated eye	0.2 - PoL	0.7 - PoL
	Fellow eye	0.025 (0.15)	0.04 (0.12)
Follow-up visit :	Operated eye	0.15 - HM	0.325 - HM
	Fellow eye	0.025 (0.1)	0.05 (0.1)

Table 26 Summary of the visual acuities for each group of patients before and after surgery.
Numerical values represent logMAR, HM = hand movements, PoL = perception of light. Values for the operated eye are ranges, and values for the fellow eye represent means, with standard deviations in brackets.

10.3 RESULTS

All subjects were able to perform the test without any difficulty on each occasion. Normality testing (Kolmogorov-Smirnov Test, Graph Pad Prism) confirmed a Gaussian distribution of the data allowing parametric statistical tests to be performed. In the scleral buckling group the right eye was affected in 16 cases, and in the vitrectomy group the right eye was affected in 17 cases. The macula was detached in 16 cases and attached in 14 cases in the scleral buckling group, and detached in 23 cases and attached in 7 cases in the vitrectomy group. Pre-operatively, the visual acuity of the operated eyes ranged from 0.025 log units to 'hand movements' for the scleral buckling group, and from 0.15 log units to 'perception of light' for the vitrectomy group. The mean visual acuity of the fellow unoperated eyes was 0.02 log units (SD 0.09) for the scleral buckling group and 0.04 log units (SD 0.11) for the vitrectomy group. The mean visual acuity of the unoperated eye did not change in the post-operative period. The mean length of time between the first and second post-operative assessment was 10.3 days (SD 1.9) for the scleral buckling group and 9.8 days (SD 2.1) for the vitrectomy group.

Repeated measures analysis of variance showed that the pointing responses for individual subjects to each of the three poles were similar during each testing session ($F=0.55$, $p=0.74$). Pre-operative data for both groups is shown in figure 61. In view of this the data were collapsed to obtain a single value of the mean pointing response for each patient, for that particular testing session. For the scleral buckling group there was a significant shift in spatial localisation of 2.9 degrees (SD 0.9, 95% confidence interval 2.5 – 3.2 degrees) on the first post-operative day (figure 62). This was statistically significant ($p<0.0001$, $t=17.9$; one sample t-test). For the vitrectomy group there was also a significant shift in spatial localisation of 1.3 degrees (SD 0.6, 95% confidence interval 1.1 – 1.6 degrees) on the first post-operative day ($p<0.0001$, $t=12.3$; figure 62). The changes observed in each of these two groups on the first post-operative day were significantly different from each other ($p<0001$, $t=7.9$; two sample t-test). At the subsequent follow-up assessment 10 days later these changes had returned towards their pre-operative values in both groups of patients (figure 63). For example, there was a small non-significant difference between the pre-

operative and second post-operative testing sessions of 0.5 degrees (SD 0.7; one sample t test, p=0.25, t=1.2) for the scleral buckling group and 0.4 degrees (SD 0.6; one sample t test, p=0.35, t=0.95) for the vitrectomy group. There was no significant difference between the changes observed in each group (two sample t test, p=0.14, t=1.4). No correlation was found between the age of the patients, their refractive error and the size of localisation changes (figures 64 and 65).

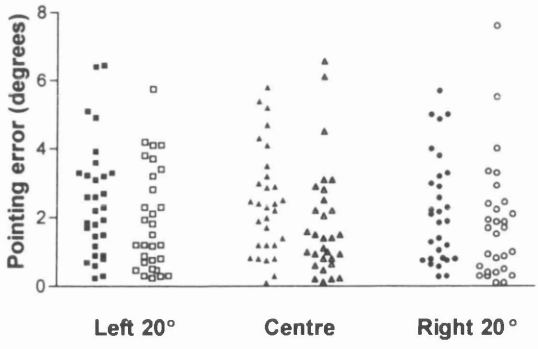

Figure 61 Scatter plot showing pointing errors at each target position for individual subjects prior to surgery. Filled symbols represent the scleral buckling group and open symbols represent the vitrectomy group. n=30 for each group for each target.

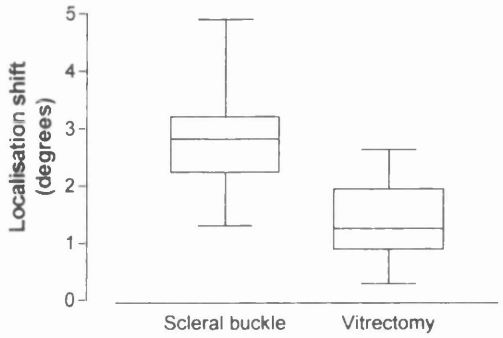

Figure 62 A 'box and whiskers' plot showing the shifts in localisation on the first post-operative day following the two different types of surgery.

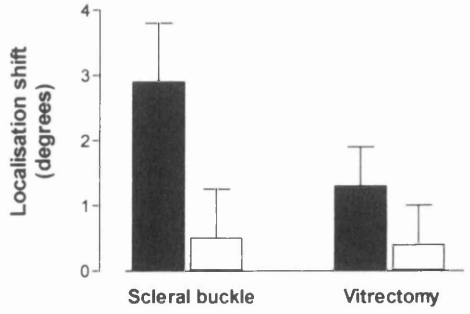

Figure 63 Bar chart comparing the changes in localisation between the pre-operative and first post-operative testing sessions (filled bars), and between the pre-operative and second post-operative testing sessions (open bars) for both patient groups. Error bars represent standard deviations. n=30 for each patient group.

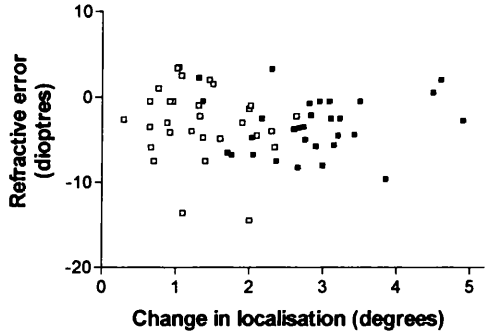

Figure 64 A plot showing the mean change in localisation of individual patients versus their refractive error (mean spherical equivalent for both eyes). Filled and open symbols represent the scleral buckling and vitrectomy groups respectively. Note that there is no correlation between these variables (r=0.1, p=0.57; and r=0.17, p=0.37 for the scleral buckling and vitrectomy groups respectively). n=30 for each group.

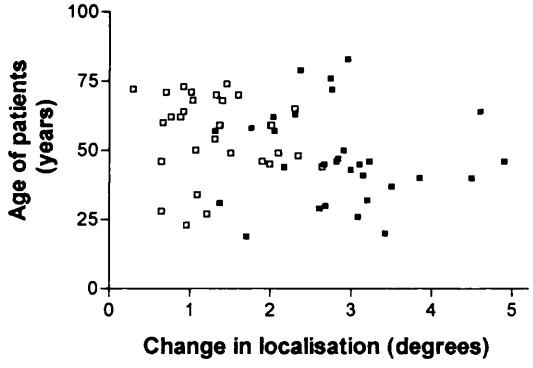

Figure 65 A plot showing the mean change in localisation of individual patients versus their age. Filled and open symbols represent the scleral buckling and vitrectomy groups respectively. Note that there is no correlation between these variables (r=0.08, p=0.67; and r=0.11, p=0.55 for the scleral buckling and vitrectomy groups respectively). n=30 for each group.

10.4 DISCUSSION

This study demonstrates that spatial localisation in patients with primary rhegmatogenous retinal detachment alters significantly more following external scleral buckling procedures compared with vitrectomy procedures, when viewing with the unoperated eye. Ideally a randomised study would have been optimal, but this was not feasible as the decision about the type of surgery to be performed was determined by the clinical status of each individual patient.

The results from the scleral buckling group are consistent with those previously reported by Campos et al [23], not only in terms of the size of the localisation shifts, but also as the observed changes had returned to the pre-operative values approximately 10 days following surgery. It could be argued that the since the buckles remain in place the changes in localisation should also persist. The fact that this was not the case is not surprising because in the days following surgery visual (ie retinal) input from the operated eye becomes increasingly available. As discussed in Chapter 2 because vision is the main source of information utilised by the visuomotor centres to determine gaze direction it is likely to take precedence over any small modification in the proprioceptive component of the extraretinal eye position signal caused by the surgical procedure.

It should also be noted that Campos et al [23]only observed alterations in four out of ten patients when testing the fellow unoperated eye. By contrast, this study found changes in all subjects who underwent scleral buckling, ranging from 1.3 degrees to 4.6 degrees. It is possible that this difference is related to the more sensitive technique employed in this study, in which pointing responses were recorded on a computer touch screen, rather than the method Campos et al [23] describe, in which the position of the target was indicated on a piece of paper. The pointing shifts found in the scleral buckling group in this particular study are of a similar magnitude to previous studies in which extraocular muscle proprioception was manipulated experimentally, resulting in mean localisation shifts of 2.5 degrees [55] and 2.98 degrees [116]. They are also in keeping with the findings of Steinbach et al [113] who observed changes following strabismus surgery, findings again attributed to modified afferent feedback from the extraocular muscles of the operated eye.

Alterations in pointing responses following vitrectomy procedures have not been reported previously. Why should these changes in localisation occur following a type of surgery that in these particular patients does not directly involve the extraocular muscles? As was discussed earlier we rely upon a combination of both retinal (visual) and extraretinal information to determine the location of targets with respect to ourselves. Since all of the patients were tested with the operated eye patched, and since the visual acuity of the unoperated eye remained the same following surgery, then an alteration in retinal information is unlikely to account for these results. This indicates that a non-visual (ie extraretinal) signal has influenced spatial localisation in the fellow eye. As was outlined above, there are two possible sources of this extraretinal information, namely efference copy and extraocular muscle proprioception.

Could the efferent copy of the oculomotor command change following vitrectomy surgery? This is possible, particularly as ocular motility problems have been reported following this procedure [120]. However, it should be noted that these changes were recorded several months after surgery and little is known about ocular motility in the immediate post-operative period. In addition, in this study testing was performed monocularly, when viewing with the normal fellow eye, and according to Walls [119] the visual system only monitors the efference command sent to the dominant eye. Bridgeman [16] also supports the concept that there is only one copy of the efferent command. Since there is no reason to believe that the motility of the unoperated eye has changed, one cannot be sure about whether efference copy has influenced the extraretinal eye position signal under the circumstances of the testing procedure. The other possible source of the modified extraretinal information is extraocular muscle proprioception. Although no muscle slings or scleral buckles were used during the vitrectomy procedures, a degree of manipulation and rotation of the globe perioperatively is inevitable. It is possible that this may have produced swelling and inflammation in the periorbital tissues in close proximity to the extraocular muscles, which in turn could have caused an alteration in proprioceptive feedback. It is also conceivable that periorbital, rather than extraocular muscle

receptors might be the source of this modified afferent signal [84]. However, there is little direct evidence to support the existence of such receptors.

Although the prime concern with patients undergoing any form of retinal detachment surgery is successful reattachment of the retina with improved visual function, some patients do complain of difficulty in judging the position of objects relative to themselves. Whilst this is likely to be related to reduced acuity in the affected eye, combined with post-operative inflammation and mydriasis, the findings of this study suggest that particularly following scleral buckling procedures, modified extraocular muscle proprioception could be a contributory factor immediately following surgery.

CHAPTER 11:
DISCUSSION OF RESULTS AND SUGGESTIONS FOR FUTURE STUDIES

11.1 Discussion of Results

The overall aim of these studies was to investigate the role of extraocular muscle afferent signals in oculomotor control and spatial localisation.

The finding that impeding the movement of one eye altered parameters of both saccadic and smooth pursuit movements of the contralateral eye demonstrates that a non-visual afferent signal, most likely to be derived from extraocular muscle proprioceptors, can under certain circumstances, influence oculomotor control. This is of importance from a scientific viewpoint, as it not only adds to our understanding of the basic mechanisms regulating eye movements, but also provides evidence that afferent feedback from the extraocular muscles can be utilised to modify the output of the oculomotor system over a very short time scale. Clinically, these results provide some insight into the compensatory changes that might occur following strabismus surgery, which inevitably involves manipulating, and potentially damaging the very areas of the extraocular muscles that are richly endowed with these sensory receptors. A better understanding of this may help refine strabismus surgery in the future.

The shifts in spatial localisation observed in the fully accommodative esotropic subjects illustrates the importance of extraretinal eye position information, (including that derived from extraocular muscle proprioception) when determining the direction of gaze. These findings are not only of theoretical importance they also have practical implications by providing some insight into the ability of children with strabismus to function with respect to their visual environment. Although relatively small shifts in localisation (up to 1.8 degrees) were found, this would equate to children inaccurately judging the position of targets by between 1-2cm at arms length. This has implications even for simple tasks in everyday life such as catching a ball or picking up a cup. Spatial localisation is an aspect of visual function that is often overlooked, and whilst the majority of children probably do not experience any difficulties, those with

strabismus perhaps warrant further assessment. The same holds true for those patients undergoing surgery for retinal detachment. It may be argued that the effects of scleral buckling surgery simply represent a nonspecific consequence of periocular trauma. However, the fact that a shift in spatial perception is observed when viewing with the contralateral eye indicates that the visuomotor control centres, in the absence of visual information, must somehow 'know' that something has been done to the operated eye. In other words, a nonvisual afferent signal must have been altered. As discussed in Chapters 1,2 and 3 our current knowledge suggests that the most plausible source of such a signal is extraocular muscle proprioceptors. Whilst a role for periorbital receptors cannot be discounted completely there is no firm evidence to support their existence. There is tendency with retinal detachment patients to equate success post-operatively with improved Snellen acuity, but as these studies show different surgical procedures can produce changes in other ways, such as in the representation of the visual world. Potentially this may compound the visual difficulties these patients often face as a consequence of their underlying ophthalmic disorder immediately following surgery.

It is of interest to note that the alterations in both oculomotor control and spatial localisation observed in these studies were either obtained under specific experimental conditions or lasted a relatively short length of time. It may well be that in the majority of individuals with normal visual function and normal oculomotor systems that vision itself, combined with efference copy is sufficient to determine eye position. In these people, extraocular muscle proprioception may have little to contribute to the control of eye movements and the representation of visual space. However, under certain circumstances of reduced or impaired vision, or in those with ocular motility disorders, afferent feedback from the extraocular muscles might assume greater significance. This is of potential importance particularly in strabismus patients, who not only have a manifest deviation, but are often amblyopic. Their greater reliance on proprioceptive feedback is likely to be compromised further following surgery, which inevitably involves the very areas of the muscles richly endowed with sensory receptors.

11.2 Future Studies

The results of these studies suggest other investigations to further elucidate the role of extraocular muscle afferent feedback in visuomotor control.

Follow up studies are planned to assess the effect of surgical procedures involving the extraocular muscles (eg strabismus or retinal detachment procedures) on the saccadic and smooth pursuit movements of both the operated and fellow eyes. In addition, quantitatively investigating the effect of different types of strabismus surgery (eg bilateral medial rectus recessions versus conventional recess/resect procedures) on these parameters would contribute to our knowledge of how such procedures affect the basic mechanisms of oculomotor control. This might also provide clinical evidence as to which operations have more favourable outcomes, which in turn has the potential to influence the choice of surgical procedure to be performed in the future.

The assessment of spatial localisation is an aspect of visual function that is not often considered in standard ophthalmic practice, but as the results of these studies illustrate it can be affected in different clinical situations. It would be of interest to investigate localisation in other groups of strabismic patients to see if their perception of visual space differs from that of normal subjects, and whether it is affected by different forms of treatment.

In conclusion, these studies have demonstrated that non-visual afferent signals, which are most likely to be derived from extraocular muscle proprioceptors, can under certain circumstances, influence both oculomotor control and spatial localisation.

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